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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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MOLECULAR AND CLINICAL GENETICS PANEL

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March 26, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

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KAREN E. WECK, M.D.	Voting Member
MARY B. MAHOWALD, Ph.D.	Voting Member
STEVEN LIPKIN, M.D., Ph.D.	Temporary Voting Member
MICHELE CAGGANA, Sc.D.	Temporary Voting Member
TERRY C. HICKS, M.D.	Temporary Voting Member
EDWARD BUJOLD, M.D.	Temporary Voting Member
LISA McSHANE, Ph.D.	Temporary Voting Member
TIMOTHY T. NOSTRANT, M.D., F.A.	Temporary Voting Member
STEVEN SKATES, Ph.D.	Temporary Voting Member
JO-ELLEN DeLUCA	Patient Representative
DAVID W. GATES, Ph.D.	Industry Representative
PATRICIA ANN FURLONG, B.S.N., M.S.	Consumer Representative
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M E E T I N G

(8:02 a.m.)

DR. PRZYGODZKI: It's 8:00. I'd like to call the meeting of the Molecular and Clinical Genetics Panel of the Medical Device Advisory Committee to order.

My name is Ron Przygodzki. I'm the Panel Chair. And my expertise is I'm a molecular, genetic, anatomic and clinical pathologist. I've got a lot of molecular testing as well as establishment of tests in my life. I currently work at the Veterans Administration. I'm the Director of Biomedical Labs and the Associate Director of Genomic Medicine Program.

I'd like to have the Panel introduce themselves with their expertise and their area.

Can we start with David, please?

DR. GATES: David Gates. I'm the Industrial Rep, and I'm Senior Director of Regulatory Affairs at Roche Molecular Systems.

MS. DeLUCA: Jo-Ellen DeLuca. I'm a 13-year rectal cancer survivor, long-time Crohn's disease survivor, about 40 years Crohn's disease, and I'm the Patient Rep. Thank you.

MS. FURLONG: I'm Pat Furlong. I'm a Patient Representative with a husband with five-year survivor of colon cancer.

DR. MAHOWALD: I'm Mary Mahowald from the University of Chicago, and I work in ethics.

DR. WECK: I'm Karen Weck from the University of North Carolina, and I'm a molecular pathologist and direct a molecular genetics laboratory.

DR. LIPKIN: I'm Steve Lipkin. I'm an associate professor at Weill Cornell College of Medicine in New York City, and a lot of my research focuses on colorectal cancer, including prevention.

DR. BUJOLD: I'm Ed Bujold. I'm a physician in private practice. I'm a solo practice physician in western North Carolina. I'm also the chief medical officer of a data extraction company.

DR. HICKS: My name is Terry Hicks, and I'm a surgeon at the Ochsner Clinic in New Orleans, and my responsibility is in teaching residents.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. CAGGANA: Michele Caggana. I'm from the New York State Department of Health. I run the regulatory program in genetics for New York State, and I direct the newborn screening program.

DR. McSHANE: I'm Lisa McShane. I'm a statistician from the National Cancer Institute.

DR. SKATES: Steven Skates, statistician at Massachusetts General Hospital and associate professor at Harvard Medical School, with a focus on early detection of cancer.

DR. NOSTRANT: Tim Nostrant, University of Michigan,

Professor of Medicine in the Division of Gastroenterology.

DR. GALLAGHER: Colleen Gallagher from the University of Texas MD Andersen Cancer Center, and I'm an ethicist.

DR. GUTIERREZ: I'm Alberto Gutierrez. I'm the Office Director for the Office of In Vitro Diagnostics and Radiological Health, and this Panel is part of us asking questions to experts. I want to thank all the Panel Members for their service. This is really important to us, and I would like to remind you that today we are actually asking you questions about the Epi proColon, and tomorrow, there will be a second part of the Panel. We're not comparing the two devices that are coming before the Panel. We want to make sure that you keep in mind that today we're just talking about the Epi proColon.

DR. PRZYGODZKI: Excellent. Thank you.

I would like to note for the record that the voting members present constitute a quorum, as required by 21 C.F.R. Part 14. I would like to add that the Panel Members participating in today's meeting have received training in FDA device law and regulation.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Epigenomics AG for Epi proColon. No other discussion on the other device, as Alberto has mentioned earlier, please. Exclusively this one.

Before we begin, I would like to ask our -- excuse me? Oh,

that's right. Okay. Members of the audience, if you have not already done so, please sign in at the station in the front of the meeting hall.

Jamie Waterhouse, Designated Federal Officer, DFO for the Molecular Clinical and Genetics Panel, will make some introductory remarks.

MS. WATERHOUSE: The Food and Drug Administration is convening today's meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the Epi proColon sponsored by Epigenomics. The Epi proColon test is a qualitative in vitro diagnostic method for the detection of methylated Septin9 DNA in plasma derived from patient whole blood specimens. Methylation of the target Septin9 DNA sequence has been associated with the occurrence of colorectal cancer.

The test is indicated to screen patients for CRC who are defined as average risk for CRC by current CRC screening guidelines. The Epi proColon test is not intended to replace colorectal screening by colonoscopy. Patients with a positive Epi proColon test should be referred for a diagnostic colonoscopy. The Epi proColon test results are intended to be used in conjunction with a physician's assessment of history or other risk factors and professional guidelines.

Based on the agenda for today's meeting and all financial interests reported by the Panel Members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

Dr. David Gates is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Roche Medical Systems.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Molecular and Clinical Genetics Panel for the duration of this meeting on March 26, 2014:

Dr. Lipkin, Dr. Caggana, Dr. Hicks, Dr. McShane, Dr. Nostrant, and Dr. Skates.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Jeff Shuren, Director of the Center for Devices and Radiological Health, on March 19, 2014.

For the duration of the Molecular and Clinical Genetics Panel meeting on March 26th, 2014, Ms. Jo-Ellen DeLuca has been appointed as a temporary non-voting Patient Representative. For the record, she serves as a consultant to the Gastrointestinal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

Before I return the meeting back over, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is 410-974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you'd like to present during today's Open Public Hearing session, please register at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

DR. PRZYGODZKI: Excellent. So I think at this point, we should move on to the Sponsor presentation. I would like to ask the Sponsor to approach the podium. And I remind the public that while this is an open session, to please refrain from commentary. If there's a need that you absolutely have to say something, please touch base with me, and we'll try and see if we can work around that.

Sponsor will have 75 minutes, and please begin.

DR. TAAPKEN: Good morning, ladies and gentlemen. My name is Thomas Taapken, CEO for Epigenomics, and in that capacity, I am responsible for all aspects of product development at the company. My academic training is in organic chemistry.

I would like to thank the FDA for giving us the opportunity today to present data generated during the development of Epi proColon, a first-of-a-kind blood-based laboratory screening test for detection of colorectal cancer.

We are also very grateful to the members of the Medical Devices Advisory Committee for taking the time to critically review the data and to discuss its implications. The data we will present today was reviewed by the FDA in conjunction with our PMA submission for the product.

Assisting the company in our presentations will be Dr. David Johnson, who will discuss the medical need around colorectal cancer screening. He will also present the results of one of our two major clinical trials. Dr. Nick Potter will describe the analytical performance of the test and then present the results of the pivotal clinical trial. Both will introduce themselves later on.

The focus of our discussion will be on the results from our assessment of our blood-based colorectal cancer screening test and the potential impact of its use in clinical practice. We see this test as potentially useful in making colorectal cancer screening available to those patients who do not adhere to screening methods according to the current standard of care. These are patients who fail to follow U.S. screening guidelines that strongly recommend participating in colorectal cancer screening.

The assumed benefits of this product, once established and

used as intended, would be an increased participation in colorectal cancer screening and, therefore, the potential for an increase in cancer detection rates in patients at treatable stages.

The core of the problem we're facing is the fact that one out of three Americans who should be screened for colorectal cancer isn't being screened today. This translates into a very simple equation. Each person not being screened equals to a 0% sensitivity test in colorectal cancer detection. While this statement might seem to be an oversimplification, Dr. Johnson will address the impact of this public health issue when he talks about the medical need for colorectal cancer screening.

On this slide you see a brief overview of the development and regulatory timeline for Epi proColon. After completion of the assay development in 2011, we conducted our pivotal trial in the second half of 2011 and initiated our modular PMA submission with the FDA in December of that year. Subsequently, in 2012, we completed a supplemental clinical trial comparing Epi proColon to a commercially established fecal immunochemical test, or FIT.

We chose to conduct this study on suggestion by the FDA and designed it with -- and discussions held with the Agency. Throughout the entire time, we were in regular dialogue with the FDA in order to ensure proper alignment of our activities with their expectations. We completed our PMA submission in early 2013.

Epi proColon consists of three different kit components. First, the Epi proColon Plasma Quick Kit, which contains the reagents for the extraction and purification of DNA from human plasma and all necessary reagents for the bisulfite conversion reaction. Second, Epi proColon PCR Sensitive Kit, including the primers and probes for the PCR detection of our biomarker. Both kits contain the necessary reagents to perform 32 determinations. Third, the Epi proColon Control Kit provides positive and negative controls to ensure proper workflow control in the laboratory.

Later on in his presentation, Dr. Potter will provide more background on the analytical features of the product from the laboratory director's perspective.

The Epi proColon test relies on the detection of methylated Septin9 gene. It's well established that epigenetic variations play an important role in oncogenesis. Epigenetic variations do not pose alterations in the underlying genetic sequence of an organism, but rather are attributable to specific changes to one of the DNA bases, cytosine, generally due to environmental or other external factors. Through this alteration, normal gene function cannot be sustained, and change of gene function leads to phenotypic variation.

Methylated Septin9 was discovered by Epigenomics scientists in a genome-wide screening approach attempting to identify differentially methylated genes in healthy and diseased tissue samples. Our assay

interrogates the 62-base pair sequence within the gamma promoter region of the v2 transcript of this gene. The gene was found to be hypermethylated in more than 90% of all colorectal cancer tissue samples analyzed. Further investigations in human plasma samples demonstrated the utility of this biomarker for colorectal cancer detection. They also confirmed that Septin9 had the highest degree of diagnostic accuracy among all the markers investigated at that time. Subsequently, this marker was trialed in more than 5,000 case controlled plasma samples both from colorectal cancer patients and healthy individuals.

Regarding the biological function of this complex gene with its multiple transcripts and splice variance, it is known that it belongs to the family of genes coding for GTP binding proteins and that it plays a key role in cytokinesis.

In order to clinically validate the product, we conducted the two major clinical studies mentioned earlier. The first, a prospective, multicenter study based on a cohort of more than 7,000 patients, will be referred to as the pivotal trial in this presentation. Results from this trial will be also presented by Dr. Potter later on. He was responsible for the testing of the clinical samples in one of the three laboratories involved in this trial and testing of all samples in our second trial.

The second trial, a prospective, multicenter, non-inferiority comparison between Epi proColon and the commercially available FIT test,

OC FIT-CHEK, will be presented by Dr. Johnson, who was one of the principal investigators of the study.

A very important part of our presentation and part of the rationale for Epi proColon is our vision of how we see this test being used in medical practice. As a starting point, patients should receive a recommendation from their healthcare provider to start beginning -- start being screened for colorectal [cancer] at their screening-eligible age. In such a setting, healthcare providers will initially be guiding patients towards standard of care, colonoscopy, in this case. If patients refuse to be screened by colonoscopy, through the availability of this blood-based test, their healthcare providers would have another option to recommend, especially to those patients who would refuse the reference method.

After a blood draw from the patient, the sample will be sent to and processed by a professional laboratory in a controlled environment. The laboratory will subsequently report the result of the test to the healthcare provider allowing for appropriate counseling of the patient in order to provide guidance for an appropriate follow-up, as indicated by the test result in accordance with the instructions for use. Most important, the entire process will be under control of professional management, which will allow for appropriate compliance with no risk of patient behavior inhibiting the proposed course of action.

This process will also, and this is very important, provide

multiple points of interaction between the patient and their healthcare provider.

Epi proColon is a simple test yielding only two possible results, positive or negative for the presence of methylated Septin9 biomarker. A positive test result should clearly result in an unambiguous recommendation to the patient to be followed up by a diagnostic colonoscopy. A negative test result, which is not a guarantee for the absence of colorectal cancer, shall lead to a recommendation to the patient to continue participating in colorectal cancer screening programs, including colonoscopy. Both of these outcomes direct the patient into the current standard of care, which leads us to conclude that the risks associated with Epi proColon testing are indeed limited.

Dr. Johnson will present his view of this conclusion further at the end of our presentation when he assesses the potential risk/benefit of Epi proColon.

Based on the data generated, which will be presented and discussed in the course of the day, we are proposing an intended use for Epi proColon as a screening test for colorectal cancer in patients defined as average risk. Clearly, we also assert that positively tested patients should be referred to diagnostic colonoscopy as the appropriate follow-up. And, lastly, we also emphasize our conviction that Epi proColon is not intended to replace colorectal cancer screening by colonoscopy.

In summary, today we will explore with the Panel the ability of a simple blood-based PCR test to identify a treatable disease. We will discuss the medical need and the impact of a blood test for colorectal cancer screening. We will present the results of two major prospective clinical trials providing evidence for the safety and effectiveness of Epi proColon. And, finally, we will offer recommendations for use of the test to complement current screening practice.

With this, I would like to turn over the podium to Dr. Johnson.

DR. JOHNSON: Well, good morning, and thank you for the privilege of being able to address you today and share some experiences that I've had in the field of gastroenterology. I'm Dr. David Johnson, Professor of Medicine and Chief of Gastroenterology at Eastern Virginia Medical School. And I'm a clinical gastroenterologist.

So in full disclosure, I'd like to say a couple things. First of all, I'm a consultant and investigator for Epigenomics. Second of all, I'm a doctor that sees patients every day, so this is my academic job. And, really, my secondary mission in life is really to provide good patient care. And, third, as a full disclosure, my wife is a survivor from breast cancer. So I have a vested interest in screening and recognize the value of screening in regards to neoplasia.

There is a variety of interests that I've developed over my career, and colon cancer screening has been one of, if not the top of the list,

my priorities since I wrote the first colon cancer screening trial in the world using colonoscopy as a preferred strategy dating back to the late 1980s. We followed this up with an initiative working with Senator Emily Couric in Virginia in the late 1990s, championing a bill to mandate colon cancer screening coverage for all covered lives in Virginia. So this has set a standard for other states around the country and really has been instrumental in getting people covered with insurance to provide necessary screening services.

I've had a longstanding interest in the academic side of this as well and served on the guidelines committees for both the Multisociety GI Task Force and the American College of Gastroenterology since 1999 and continue to serve in those capacities writing the guidelines, co-authoring the guidelines for colon cancer screening, and setting standards for insurers and for the physician providers.

I've had a longstanding interest, also, in the academics, have published hundreds of articles, but the primary interest is, as I noted, in colon cancer screening, and also serving in a variety of leadership positions in a vested way from executive boards and the board of trustees for agencies like the National Quality Forum, currently with the American Board of Internal Medicine and the American College of Gastroenterology, and was privileged to serve as the president of that organization from 2006 to 2007.

It comes down to a function of really all about getting the

message out, and today, my job here and goals are really to conceptualize for you and put in context as a clinical side of what the opportunity to add a new screening test to colon cancer screening and really what this may mean as we move forward in trying to narrow the gap, if you will, as far as getting more people into the screening system.

This is a publication that was put out just a couple months ago from the CDC. And they have an initiative called Disparities in Health, and Disparities in Cancer is a secondary initiative of that as well. But it points out a couple things that are really key. First of all, about 90% of patients live five or more years when their colorectal cancer is found early through testing. So, again, we talk about early testing and recognizing survival is incumbent on early detection.

The unfortunate thing is that they also report that 1 in 3, as Thomas has already alluded to, about 1 in 3, or 23 million people that are currently in need and eligible for colon cancer screening actually have not been screened. And this is clearly a target area for today's discussion.

And also the aspect that ways that people can have convenient ways of screening. In particular, things that people could even do at home, like stool testing, only 1 in 10 are currently using this type of modality as well. So there's clearly an unmet need of getting through to this target audience -- target area of 1 in 3 that have yet to have been screened. And we do know that irrespective of getting something done, it's really a function of getting

something done, and the best test is ultimately the one that gets the test done if it's not going to happen any other way.

Well, I've got some good news, and I've got some bad news. The good news is that U.S. cancer statistics, we do see over the last three decades tremendous progress as it relates to colorectal cancer, and the initiatives clearly have accelerated over the last decade and a half, where we've had better availability of coverage for colon cancer screening. And we've seen a decrement of nearly 30% over the last two decades as it relates to colon cancer mortality in the U.S.

The bad news is it's still an incredibly prevalent disease. And when we look at the U.S. population, it's striking how numbers of patients that still have opportunities are not using these opportunities to get screened. And if we look at the number of deaths in the U.S., it's the second leading cancer-related death still in this country. It equates to nearly, still, 142,000+ new incident cancers in the colon per year, and this equates to nearly 51,000 patients that die from a potentially preventable disease.

We heard that there are some survivors in the Panel, and I'm sure everybody in the audience has a vested interest in a survivor, and somewhere it's touched the life, as it has in mine, as far as early detection. And early detection means enhanced survival.

This is very resonant when we look at colon cancer in particular. Stage 1 is the early side of colon cancer. Stage 4 is the

consequent late stage and advanced stage of colon cancer. And we do know that survival incumbent on the detection is really tied to the early detection of earlier stages of cancer. As such, it's a very treatable, if not curable, disease even in the early stages of cancer. A lot of things that we do for colon cancer prevention are to prevent it, but when we discover it early, it's still a very curable disease, with 90%-plus cure rates even for the early stages of cancer. Late stage therapies are improving but still abysmal at the present time.

The modalities that we presently have in the United States, and is recommended by guidelines, look at a variety of different testing modalities. One is the testing modality using fecal testing as it relates to fecal occult blood, or more recently, the advances on this using the immunochemical or FIT test has really replaced the fecal occult blood test, less false positives. Stool DNA is a topic that will be discussed by you all tomorrow, but another stool-based testing that certainly has been cited in the literature.

And then we have the endoscopic modalities, colonoscopy being the gold standard, but flexible sigmoidoscopy clearly has value. It's used more often outside of the continental United States, but clearly, evidence and screening guidelines incorporate this as a modality among the choices that we have for colon cancer screening and prevention. And the same for radiologic description of CT colonography or CTC or virtual

colonoscopy, as some have alluded, as well as barium enema, the latter being somewhat replaced as prioritization in guidelines, but nonetheless, beyond today's discussion focusing on radiologic issues we will not [discuss].

Now, the most common cancer tests in the U.S. are really, as I alluded, colonoscopy and fecal testing as it relates to FOBT, now conventionally more replaced by FIT. The reference standard is clearly the gold standard. It's not all polished gold, and colonoscopy has its own incumbent risks, so we do know some variance is there even in performance standards. But, nonetheless, it is the standard of care, and it is the standards by which other modalities are recognized and held accountable as the index standard.

National guidelines have looked at these modalities and recognized that even among the modalities available, not always are all included in recommendations. So, in guidelines, what typically is done is the evidence in there. They weigh the evidence, the strength of the evidence, and then the strength of the recommendation. And there is clearly available technologies that are out there even still today that have not been ushered in, at least uniformly in the guidelines as far as official recommendations for screening for the U.S. population.

The American College of Gastroenterology is the one that specifically recommends colonoscopy as the preferred strategy as it relates to colon cancer screening and prevention.

Now, as we say, getting the message out is really a priority, because people need to hear about this. And we've done a much better job through the lay press, through patient advocacy and physician advocacy groups in getting the message out. Colon cancer screening rates have improved, but they still remain suboptimal.

We've seen a progressive improvement in colonoscopy screening because of legislations, and we've seen a deterioration, at least, and probably replacement of the fecal testing because of preferred strategies with endoscopic means. But, nonetheless, what is somewhat alarming to us is over the last decade, we've improved, but over the last three years, we've plateaued. We really have not seen a significant increase, but about 1% a year over the last three years as it relates to colonoscopy utilization in this country.

The Health and Human Services in conjunction with the CDC set a goal by 2018 suggesting that 80% of people should be screened for colon cancer. That's a sizeable goal. And there's a sizeable gap here if we look at where we are at present, look at the rate of the line of ascension for colonoscopy. And there's clearly a gap analysis that begs for how do we get there with present technology or the present pathways that are available to patient screening.

Well, it's all about closing the gap, and screening is about saving lives, and survival requires early detection or requires detection at all.

And detection requires participation, because if we're talking about screening rather than symptom-directed testing, we have to have the patients' willingness to participate. And the pathways to participation are really the key because we're just not quite there yet. As you saw, the ascension and the plateau, we've got a gap that needs to be closed; how do we get there?

But we do know that there are a variety of things that influence participation. One is choice. And clearly there is literature that supports this very strongly, that when patients are given an option list, they can individually select with in concert counseling from their physician or their care provider. That leads to increased participation in programmatic screening.

We do know that, too, the patients will invariably have some preference. They'll listen to care providers. And they'll be counseled about that, but participation and giving some preferential options to patients may increase also the willingness to participate. And that's very important. And we do know, too, that the innovation or ways that present technology has changed or that new technologies are delivered or pathways of communication requiring innovative strategies for deliverables will increase participation as well.

It's all about closing the gap. And that's the point. We need more options. We've got a gap to close. And we're here to talk about how to get there.

Thank you very much.

DR. POTTER: Good morning, everybody. My name is Nick Potter, Chief Scientific Officer and Director of Molecular Diagnostics at Molecular Pathology Laboratory Network. I'm an ABMG-certified clinical molecular geneticist and hold certificates of qualification in bacteriology, virology, molecular oncology, and genetics from the New York State Department of Health. I am also licensed as a laboratory director in the state of Tennessee.

I have practiced in the clinical diagnostic space for 23 years, directing CLIA high complexity laboratories in both academic as well as private commercial settings. And I currently hold the academic titles of Clinical Associate Professor of Pathology at the University of Tennessee Medical Center and Clinical Professor of Pathology, Quillen School of Medicine at East Tennessee State University.

In the last line of its Executive Summary, the FDA refers to this test as "first-of-a-kind." This is indeed the first medical device of its kind developed for the stated intended use. However, despite Epi proColon's novelty, it utilizes and exploits mature, well-understood, and routine molecular technologies, methodologies, and instrumentation. And it can easily be integrated into a CLIA high complexity molecular laboratory.

In the first part of my presentation, I will briefly walk you through the use of the Epi proColon test, outlining some of the test processes

and workflow. I will also present the nonclinical data.

The Epi proColon test was developed to detect methylated Septin9 in DNA extracted and bisulfite converted from 3.5 mL of human plasma. The test is designed as a qualitative, duplex, real-time PCR specifically targeting Septin9 as well as a sequence within β-actin, the latter of which is targeted as an internal control to assess specimen integrity and PCR performance. A valid result is generated as either Septin9 positive or Septin9 negative based upon predetermined clinical cutoffs and a valid β-actin cycle threshold value.

In this example, on the right, the Septin9 positive result is presented in red. Had the result been negative, the red line would have been below the threshold, indicated as a dotted line. An invalid result would be indicated by β-actin curve that crosses the threshold at late cycle numbers beyond the empirically determined cutoffs or not at all. And, finally, the entire process is monitored by both positive and negative process controls.

Analytical sensitivity and limit of detection was determined by using Septin9 methylated DNA spiked at various concentrations into either human plasma or an artificial matrix. The 95% LoD was determined by regression analysis as 4.7 pg/mL with confidence interval as shown. And this concentration corresponds to approximately one genome copy of methylated Septin9 per mL of plasma.

Precision and reproducibility were assessed by repeatedly

testing aliquots from a 14-member panel consisting of plasma pools from CRC patients and self-declared healthy blood donors. Variability was challenged and assessed by testing at three sites with six operators, two per site, using three different lots and three PCR machines. The agreement with the expected test result in replicate testing for all CRC pools was 98%. And the agreement with the expected test result in replicate testing of three healthy donor pools was 75%.

Now, we saw this 75% agreement in replicate testing of healthy donor pools, and quite frankly, it raised a legitimate question regarding analytical specificity. So, to determine root causes for this cross-reactivity, several assessments were performed.

First, to rule out analytical false positives due to inherent assay design considerations, in silico analyses, electronic PCR BLAST were performed. These demonstrated that only the Septin9 target sequence was predicted to amplify.

Second, probe specificity for the Septin9 target was empirically demonstrating using synthetic templates.

Third, simulated samples containing unmethylated DNA were tested, and they tested negative.

And, finally, in plasma samples where Septin9 positivity was observed by Epi proColon, the presence of methylated Septin9 target sequences were confirmed by another method, bisulfite sequencing.

So, to summarize, these data demonstrate that the Epi proColon test is analytically specific for methylated Septin9. And, in short, the 25% positive results observed in the reproducibility study in healthy pools confirmed that. These results truly reflect the presence of trace amounts of methylated Septin9 in these specific pools.

Potentially endogenous and exogenous interfering substances were tested at biologically relevant concentrations. No interference was reported. At intentionally elevated concentrations, false positive results were detected for human albumin, human sperm DNA, and red blood cells.

Assay robustness was challenged by failure mode and effectiveness analysis. Twenty potential modes representing pre-analytical, including DNA extraction, bisulfite conversion, DNA purification, as well as analytical variables, PCR, were tested. And, in all challenges, the assay performed correctly or controls indicated the failure.

Robustness of blood and plasma handling, preparation, and storage were also assessed, with no significant impact on test results.

Hence, the analytic results support the assessment of Epi proColon as a robust and accurate test.

The pivotal clinical study was a prospective study aimed at assessing the clinical performance of the Epi proColon test as a screening tool in a cohort of screening-eligible subjects. The primary objective of the pivotal trial was the detection of colorectal cancer by Epi proColon compared to the

reference standard of colonoscopy with histological confirmation. The performance targets were 65% sensitivity for CRC, at 85% specificity.

And the secondary objective was to evaluate test positivity in clinically defined subgroups. These subgroups consisted of CRC by stage, Stages 1 through 4; advanced adenomas, adenomatous polyps greater than 10 mm and adenomas with a villous component or high grade dysplasia; small polyps, polyps less than 10 mm and without a villous component or high grade dysplasia; and samples with no evidence of disease.

Study samples consisted of those archived from the PRESEPT trial, which incidentally stands for the Prospective Evaluation of Septin9 performance in CRC screening. The PRESEPT trial enrolled 7,941 subjects from an average risk CRC screening-eligible population. Patients were enrolled until the target of at least 50 colorectal cancer cases was met. The trial was conducted at 32 sites, 22 in the United States and 10 in Germany. The Epigenomics pivotal study evaluated 6,857 archived plasma samples for which information was available.

Patient inclusion criteria for the pivotal study were similar to those for the PRESEPT trial and are noted here. Note that one requirement for all participants, no matter what the age group, was that this was to be the first ever colonoscopy.

Now, as you'll see in a minute, the average age in the trial was 60.5 years, suggesting that the study population reflected a group of patients

who had delayed following recommendations -- recommended guidelines -- and resembled, in this way, a group of real-world patients who were unwilling or unable to participate in colonoscopy or who had simply not done so for whatever reason.

The exclusion of high-risk patients followed the guidelines of the U.S. Multi-Society Task Force on Colorectal Cancer to create an average-risk study population. And the PRESEPT study enrolled a broad demographic range of subjects representing similar numbers of both genders, subjects of different age, the average age being 60.5 years, and ethnic minorities.

As mentioned earlier, a cohort of 6,857 plasma samples from the original enrollment were available for evaluation in the pivotal trial. The distribution of samples by clinical subgroup is presented here along with the three primary reasons for subject unavailability, which were failure of inclusion or exclusion criteria, incomplete colonoscopy data, and insufficient sample amount. The pivotal trial was designed to demonstrate performance in terms of clinical sensitivity and specificity.

Accordingly, we tested all CRC samples for assessment of sensitivity as well as approximately 1600 non-CRC subjects comprised of all available advanced adenomas and random subsets of small polyps, as well as samples with no evidence of disease.

The total number of non-CRCs were chosen to generate a specificity estimate, with high precision. And specificity was calculated from

samples selected based upon a random sampling approach, ensuring that all demographic groups were represented. Thus, for the determination of performance characteristics, all 50 CRCs, 650 advanced adenomas, and subsets of 454 small polyps and 469 samples with no evidence of disease were tested.

For testing, the samples were randomized, deidentified, and shipped to three independent U.S. laboratories. And after testing was completed at all laboratories, the test results were reported to the Sponsor who performed the statistical analysis and reporting of the final results.

A total of 1,544 valid test results were obtained from 44 CRCs and 1500 non-CRC samples for estimation of clinical sensitivity and specificity, respectively. As reflected here, the trial design resulted in an under-representation of small polyps and samples with no evidence of disease. Hence, the analysis presented on the next two slides will take this under-representation into account.

The Epi proColon test detected 30 out of 44 cancers, for a sensitivity of 68.2%. 1182 out of 1500 non-CRC cases tested negative, for an observed specificity of 78.8%. Weight of adjustments, however, to the U.S. census data generates a slightly different specificity value of 79.1% while adjustment to the PRESEPT patient cohort resulted in a specificity estimate of 80%.

The trial results met the sensitivity target of 65%, which was

set a priori based upon the performance of a prototype Septin9 assay. The lower bound of the confidence interval was below that target, however, but the success criterion was formulated as a point estimate. The trial results, however, were below the specificity target of 85%. Again, this target was set a priori based upon the performance of a prototype Septin9 assay. However, internal risk/benefit analysis with assessment from external medical advisors led Epigenomics to conclude that there was significant clinical merit in a CRC screening test with these clinical characteristics to continue. Discussion of the question of clinical value will be offered later in the Epigenomics presentation.

Secondary analysis addressed test positivity in different non-CRC groups. Epi proColon showed no discriminatory ability or relevant detection of small polyps or advanced adenomas compared to the overall positivity of 21.2% of all non-CRC samples.

We also evaluated Epi proColon's ability to detect cancer by stage. The point estimates and confidence interval for cancer detection by stage demonstrate that the test detects cancer at all stages, 1 through 4.

Epi proColon was also equally informative for the detection of cancer by tumor location, proximal versus distal, right versus left.

Now, up until now, I've described the clinical performance of Epi proColon in terms of absolute sensitivity and specificity. And while these performance characteristics are useful in the context of defining the test

accuracy, they're really not that instructive in the context of defining clinical outcomes, a calculation extremely important to both patients and their practitioners. As such, it's often useful to present data in terms of diagnostic likelihood ratios, or DLRs. And DLRs are used to assess the clinical value of a test result using sensitivity and specificity data to determine whether a result usefully changes the probability that a disease is present or absent. Mathematically, a value of not equal to 1 defines the relative likelihood of the presence or absence of disease.

So, here are the pivotal trial results in terms of diagnostic likelihood ratios. The positive DLR of 3.4 means that if a patient tests positive, that patient is 3.4 times more likely to have colorectal cancer. Conversely, negative DLR of 0.4 means the patient who tested negative is 2.5 times less likely to have colorectal cancer. And both the positive DLR and the negative DLR differ substantially from 1.

Now, let's turn the attention to specific demographic factors in which statistically significant influence on test specificity was observed. And that would be age and ethnicity.

This table shows the data broken into three age groups. The specificity decreases with age. However, even in patients greater than 69 years of age, the positive DLR is informative. A patient over 69 who tests positive is 2.6 times more likely to have colorectal cancer. Conversely, a patient who tests negative is 2.4 times less likely to have colorectal cancer.

Now, this table shows the data broken into three groups based upon ethnicity. There is reduced specificity in the African-American cohort. Yet again, the positive DLR is informative. An African-American patient who tests positive is 2.5 times more likely to have colorectal cancer, whereas an African-American patient who tests negative is 2.2 times less likely to have colorectal cancer. So, clearly, analysis of data using DLRs provide potentially actionable clinical information.

So, to summarize and conclude, Epi proColon has a sensitivity of 68% for the detection of colorectal cancer at a specificity of 80%. There was no significant detection in advanced adenomas or small polyps above the level of detection, in samples with no evidence of disease. The test detects CRC at all stages, with clinical sensitivity for treatable disease Stages 1 to 3 of 64.1%. The Epi proColon test is equally sensitivity for CRC detection in the right and left colon. And last, though the false positive rate varied between demographically defined groups based on DLRs, Epi proColon provides potentially actionable information to patients of all subgroups analyzed.

And in his risk/benefit presentation, Dr. Johnson will comment specifically on the clinical value of these test results.

Thank you very much for your time, attention, and consideration this morning.

DR. JOHNSON: Okay. In my first discussion with you, we talked about some of the medical needs for new testing and expanding the options

that are available to colon cancer screening. Dr. Potter presented the pivotal study. And my goal for the next few minutes is just to share with you the follow-up of the confirmatory non-inferiority trial with the Epi proColon versus the OC FIT-CHEK.

The development here, or the rationale, was to provide really the data to support this from the pivotal study's data that was presented previously. The comparison here was to be with FIT, and this is a test that is in guidelines as a routine recommendation for stool-based testing, and the preferred strategy relative to fecal occult blood testing at present day.

The OC FIT-CHEK was used and selected particularly because it's one of the top-performing FIT tests that's commercially available in the United States, so a high performance, high utilization, and standard commercialization availability in the United States.

The objectives are really as it's stated, to show non-inferiority of the clinical performance then of this Epi proColon versus this OC FIT-CHEK. And the design was a multicenter trial, prospective evaluation comparing both the Epi proColon and the OC FIT-CHEK to colonoscopy, as mentioned earlier, as the reference gold standard for colon cancer detection.

The subjects were 100 screen-detected patients with colorectal cancer, 200 average-risk screening-eligible patients, and the goal, as I stated, were non-inferiority with margins set for 10% for sensitivity and 20% for specificity. The analysis was a two-sided analysis for sensitivity and

specificity, and then the differences were compared to non-inferiority margins.

The trial design was 61 trial centers around the continental United States. Group A was the post-screening colonoscopy patients. So, these are patients that had a cancer or a high suspicion for cancer and were going to surgery for surgical resection, and blood and stool specimens were collected 10 or more days after that index colonoscopy. Group B, then, were the patients that were undergoing screening colonoscopy. And this was a prospective evaluation, procurement of blood and stool specimens prior to their bowel prep in the index colonoscopy. These were then all submitted to blinded independent laboratory testing for their analysis.

The criteria were similar as far as inclusion and exclusion to the pivotal study. Group A, however, had an additional requirement. This required a colonoscopy diagnosis, as you would expect, for the diagnosis of colon cancer and the histologic confirmation as it was confirmed at the time of surgery.

The subjects tested: There were 290 subjects with paired plasma and stool specimens. Of note, 11 additional subjects were included in the analysis because only the plasma, and not the stool specimens, were able to be submitted and procured for inclusion.

Demographics were balanced across the age and gender and ethnicity, and the data is shown here, as across the endpoints of cancer and

non-cancer, including values for advanced adenomas and small polyps and no active disease.

The primary endpoints are shown here in the gray. What we see is the comparison for the Epi proColon. And this is all the Epi proColon, so it includes those 11 patients for which there were no paired specimens for the stool specimens. And then the sensitivity and specificity are shown in the orange and green graphs comparing the two.

Comparing for non-inferiority, the sensitivity was met for the Epi proColon with the FIT, and specificity was not. So sensitivity met the objectives as it relates to the point estimates of -4.2 for differences in sensitivity within the predetermined non-inferiority margin of 10%. The upper bound of the confidence intervals of 8.1% was inside the 10% margin. The specificity, however, for non-inferiority was not met. And the point estimate of 16.6% for difference in specificity within the predetermined non-inferiority margin of 20% was evident. And the upper bound of the confidence interval of 22.9% was outside the 20% margin that was preset.

Now, as Dr. Potter talked about, likelihood ratios, this is something that's very important for me as a clinician. So there was a difference in the positive likelihood ratios being higher for the OC FIT-CHEK. And that, in fact, is an issue that is an advantage to me, because if, in particular, I get a patient in that's going to be screened that wouldn't have been screened another way, I want to know that that screening at least has a

likelihood of excluding cancer. And this is where the negative likelihood ratios were comparable to the FIT-CHEK. So when a patient that I couldn't get in gets screened, at least I have some relative confidence that they, in fact, have a negative test. I wouldn't have access to screening them otherwise.

The default is if I get more people in on the positive likelihood ratio, and they ultimately don't have a colon cancer, what does that mean? Well, it means that I got them into a check that they wouldn't have had otherwise and they would have started with had they followed our recommendations for the preferred strategy for colonoscopy. So having a safety net that defaults to increased detection not only of cancer, but of precancerous polyps is of value.

As it relates to the matched samples, there are some other interesting comparisons here, because as this slide, this two-by-two table illustrates, in some situations where cancer was evident, there was a difference for detection with one test versus another. In the OC FIT positive, there were 16 that were Epi proColon negative. And, conversely, in the OC FIT-CHEK that was negative, there were 20 cancers that were Epi proColon positives. One shoe doesn't fit all in cancer.

As it relates to location, Dr. Potter alluded to this in the pivotal study as well, one of the key things that we're concerned about is detection of cancers across the spectrum of the demographics of the colon. We want

to see right and left colon cancer detections. We find that there's an increasing prevalence of missed cancers in the right colon. So a test needs to be comprehensive, including both the right and left colon. And in this circumstance, there were no differences as far as non-inferiority across the spectrum of colon cancer, right and left colon included.

It's important, as I alluded to earlier, to detect cancer at an early stage. Survival is relative to early stage of detection, and cure is achievable even in the early stages of cancer. And in the non-inferiority comparison here, the good news was that there was no difference either as it relates to the Epi proColon or the OC FIT-CHEK.

So, in summary, what I would propose to you and conclude, the sensitivity data for non-inferiority for the OC FIT-CHEK was evident. The specificity data was non-inferior -- was not statistically significant as it relates to the OC FIT-CHEK. The clinical performance was, in fact, though, consistent with the pivotal trial study results, with the sensitivity of 73.3% compared to 68.2% in the pivotal study, and the specificity as it relates to 81.5% versus 80% in the pivotal study.

So, both tests performed equally well to confirm the absence of colon cancer; in particular, the negative likelihood ratios of 0.33 were virtually superimposed and exact. It identified a number of cancers, and in fact, it didn't represent that all cancers were identified equally by the other -- by each test. So there was some variance in detection between the two

tests in the same individuals.

Consideration of this as it relates to combining tests or doing a joint testing with different modalities is beyond, in my mind, today's discussion and certainly would be a subject that would be of interest for screening and writing guidelines when they look at the data and make recommendations officially on this type of proposal.

Clearly, it was evidence as well that colon cancer detection was evident at all stages, again, reflecting that early stages and late stages both were detectable and non-inferior for the two comparisons today. And as stated also, importance to detect across the colon in toto, right and left colon cancers were equally detected across both of these non-inferiority comparisons.

Thank you very much.

DR. TAAPKEN: So, based on the data presented today and the medical need around colorectal cancer, we are suggesting a labeling of the product which would reflect safe and effective appropriate -- sorry -- safe and appropriate use of this product. In our intended use statement, we are making these key statements.

First, the product shall be used as a screening product for colorectal cancer. The rationale for this claim resides in the fact that 35% of the screening-eligible population in the United States currently remains unscreened. Being a simple laboratory blood test, Epi proColon can address

this public health problem quite effectively. Furthermore, the data presented today supports, in our view, the proposed intended use.

Secondly, we are clearly advising that positively tested patients should be referred to a diagnostic colonoscopy. As a screening test, and like with most screening tests, a proper diagnostic follow-up, according to the established standard of care, is indicated. In our case, that's colonoscopy.

The third element: Results generated with the Epi proColon test should be assessed in conjunction with the entire patient background information and history available. Again, we want to ensure appropriate patient management under professional supervision given the severe implications of colorectal cancer as a disease.

Along with this intended use, we proposed a number of warnings and limitations to be issued in conjunction with using this product. The key warnings include, first and foremost, the test is not intended to replace colonoscopy. Not only is colonoscopy the reference standard for colorectal cancer screening, according to most of the guidelines published, as Dr. Johnson showed, but it also represents the first step towards a possible treatment under professional supervision. That is why it's so important.

Secondly, positive test results are not confirmatory evidence for the presence of colorectal cancer. While this statement addresses the observed specificity in our trials, it also makes clear that a screening test cannot be a replacement for an appropriate diagnostic follow-up.

Third, a negative test result are not confirmatory evidence for the absence of colorectal cancer, and patients should be counseled to continue to participate in colorectal cancer screenings, including colonoscopy.

We believe the data in our trial show that Epi proColon does not detect all cancers. Obviously, it doesn't. Hence, there cannot be a definitive assurance through a negative test result. Beyond this, cancers can also develop even after definitive proof of their absence, and this is why it is so crucial to continue participation in a screening program in any case.

In our limitations, we highlight the relevance of the test especially for average-risk patients who are unwilling, unable, or do not participate in established screening programs and according to the established guidelines. The purpose of this limitation is to steer patients away from the test who already are compliant and especially encourage the use of the test in a non-adherent population.

In our limitations, we also clearly express the current lack of long-term efficacy data for the programmatic use of Epi proColon.

In addition to the intended use statements, warnings, and limitations, Epigenomics has developed a comprehensive set of materials for healthcare professionals, laboratories, and patients to ensure the appropriate use of the product according to its instructions for use.

Now, let me briefly address this last point made around the

current absence of longitudinal data supporting programmatic use of Epi proColon. In discussions with the FDA, Epigenomics has considered a clinical trial which would be designed to obtain longitudinal performance data on the test in the intended use population.

In the proposed study, we would aim to investigate the diagnostic yield, test positivity as measured by predictive values, programmatic sensitivity, and screening compliance with Epi proColon; also, adherence with diagnostic, so in this case, colonoscopic follow-up upon positive test outcome will be investigated. We are currently suggesting three annual consecutive rounds of testing followed up with colonoscopy for negatively tested subjects two years after the last negative test result. Endpoints shall be specified with statistical significance.

While the final study design and objectives are still under discussion, at this point, we cannot make statements with respect to final study subject numbers since these are obviously dependent on power calculations based on the inputs from these discussions. However, I want to state clearly that it is our intention to appropriately study the use of Epi proColon in a programmatic screening setting once the product is in use in the targeted population.

I would like to turn over the podium again to Dr. Johnson.

DR. JOHNSON: Well, thank you. And I'd like to just take a few minutes just to put in profile a risk/benefit analysis to give some context as

to how we value things when we do tests and how we do procedures and how we really live life. Everything should be subject to some type of risk/benefit analysis going forward.

As it relates to today's discussion, the potential risks for risk/benefit, one would be off-label use. To me, that seems to be addressed by Dr. Taapken's comment here about education and labeling and things that the Sponsor would have responsibility for if this occurs, but again, not without education and direction or potentially to be guided.

The procedural risk of a blood draw, to me, is fairly de minimis. Patients get this every time they come into a physician's office if they have some serum testing. So, again, I dismiss that as a procedural risk intrinsic just to the procurement of the test.

What I'd like to spend a little bit of time, as it relates to the false negative and false positives, because again, I think as a clinician, this is where it really plays out for me, and I'd like to give you my views on how this may play out as it plays out into making this a commercially available option. One of the false negative analyses that the Executive Summary from the FDA was taking a population of 100,000 proposed subjects and assigning the prevalence that was defined in the pivotal studies and looking at 0.7%. Well, with that, we'd hold again to the scenarios of no screening, colonoscopy, the Epi proColon, and the FIT-CHEK as the scenarios that they could then look into the longitudinal assessments, the false positives and false negatives, and

look at this in the cancer patients and the non-cancer patients.

Well, if we talk about no screening as a backdrop, that's the 700 patients that get cancer with no screening. That's a default that means they were avoidable, but potentially not discoverable, because the patients wouldn't accept the screening modality.

If we look at the colonoscopy and say the true positives were 700 -- that's 0.7% -- I will tell you that it's not exactly the polished gold that we'd like it to be, and in fact, there's an article that's coming out next week in *Gastroenterology* that cites the prevalence -- or 6% missed cancers by colonoscopy. So, even in the best of hands, because of the element, unfortunately, of human error or detection strategies, it's not as perfect. But for this model, we'll assume that it caught all 700 cancers. And then the true positives for the two tests that were being discussed today, certainly, those are cancers that are good news, we found them, we hopefully found them early. And then there are false negatives that are, unfortunately, by nature of the beast relative to -- that's the value of testing, and some tests are better than others.

But I want to focus on the false positives, because the false positives here, meaning the patients went in, they got a test, and they got colonoscopy, but they didn't have cancer. Well, if we default and say that now 19,000 of these patients came in and got colonoscopy, that's where I wanted you to start to begin with. If we use the endpoint of cancer, that's,

again, a late stage of diagnosis. It's really not screening.

But if we don't discuss for today, necessarily, the added value of finding precancerous polyps, which, oh, by the way, was approximately 40% of this study, we've now entered into a scenario of prevention, where these patients hopefully would have been there to begin with, they didn't get in, and now we've got them into a default where they're potentially now following more closely with colonoscopy. And they didn't have cancer, but may have well had precancerous polyps.

If we look at precancerous polyps and the background prevalence in the United States, the National Quality Forum and CMS will accept this, is going to set a minimum threshold of 20% of patients with prevalence of polyps, adenomatous precancerous polyps when they go to an index colonoscopy. That number, I will tell you, is very low. It was set low because it's a starting point. If you look at expert colonoscopists, the numbers are probably closer to 40%. So, the prevalence of precancerous lesions is very high. The more we can do to take these out and remove them removes that index risk from that precancerous polyp. So, it's a good thing to increase colonoscopy utilization and removal of precancerous lesions.

If we talk about a false negative, it's consistent that the patient that didn't get screened would be the ultimate default. So, you've got 700 cancers out there. So, if we take a test that's inferior to colonoscopy, that's the non-invasive test, they clearly have an elevated risk. Why? Because they

miss cancers by nature, but they certainly at least didn't miss all 700, and they caught a sizeable percentage of those that wouldn't have been screened otherwise had they not entered into a screening strategy.

And the negative likelihood ratio is what I alluded, to me as a clinician, is the most important. I didn't get the patient in. Now I got him in. At least I have some relative confidence in here non-inferior to the FIT-CHEK that that patient, in fact, does not have cancer. Relative to the OC FIT-CHEK, there was no elevated risk relative to a negative result therefor. These were non-inferior and, again, consistently across the board equal.

As it relates to false positives, the positive Epi proColon and a negative colonoscopy, I alluded to, that to me, is not necessarily a bad thing. It may actually, well, be a good thing. The patient's certainly now in a colonoscopy strategy and screening if they've had precancerous lesions detected at the time of colonoscopy; again, another good benefit as it relates to driving more people into the colonoscopy.

It would be inappropriate to ascribe any type of adverse events from a colonoscopy to the index test, because again, the patient wouldn't have been there to begin with. If they had a screening colonoscopy, the relative risk from screening colonoscopy, we never say never, but it's incredibly de minimis. And screening colonoscopy complications are almost as close to zero as we can make them. And the attributable risk would not be tied to the index test. It would be tied to the colonoscopy itself, where they

should have started to begin with had they followed a preferred strategy.

In fact, the experts on the Panel would attest, too, that the large majority of colonoscopy serious adverse events are entirely related to clinically indicated interventions. So, in the screening colonoscopy trials, the relative complication rate approaches 1 in 3,000 or less, and if you -- in experts' hands, you will look at the published trials for screening colonoscopy, there are no purported perforations. We never say never in anything we do in life, but in screening studies, the perforation rate is essentially as low as we can make it close to zero.

Perforations being said, patients are, again, relative to standard of care, now in the hands of or under direction of the colonoscopy screening, and they certainly have now achieved at least what we'd view as the standard of care.

As an overview, I'd like to conclude that Epi proColon provides, to me at least, the data overwhelmingly -- it's the first effective blood test as we relate to detection of colon cancer. It certainly has manageable risks. We've talked about these in a way that looks at the false negative and false positives in particular, and it may, in fact, increase screening participations. We're talking about serum-based testing. And, again, something that is very cultural to patients coming to a care provider's office. When they leave, it's invariably they're sent to a lab, and that closure, the gap analysis of getting the test done is really the final endpoint in this. Not just I as a care provider

recommended it, I sent you home with a test or you come back for a test. It's the gap closure that as you leave the clinic, you have your test performed. And, again, how we get that gap closure towards that 80%, and we're plateauing it at the 65% range now, we certainly have an ACS goal set by 2018, and we need some gap closure for sure.

Blood testing, as I said, is routine. It's cultural. It's expected. And the completion rate among recommended testing as patients leave the clinic or office is invariably close to 100%, if not that. An additional non-invasive test, therefore, would be a very logical choice in inclusion of the menu of options for colon cancer screening.

And it's very appropriate as we close the month of March. We're talking about colon cancer screening month. How appropriate is it that we're finally looking at another gap closure today and talking about expanding the options and closing the gap.

Thank you very much.

DR. TAAPKEN: Thank you, Dr. Johnson. We have finished the presentation. We would like to thank you for your attention. And I wanted to highlight that, apart from the speakers, we have two of my colleagues here, Dr. Gunter Weiss, who's sitting over there, together with Dr. Uwe Staub. Dr. Weiss will be able to speak to clinical data and biostatistics should there come questions in that direction. And Dr. Staub can speak to assay development and biologics.

DR. PRZYGODZKI: I would like to thank the Sponsor's representatives for the presentations. I would like to note to the Panel that we do have an open Panel discussion, but if there are any immediate questions that we would like to ask the Sponsor at this point, please go ahead.

Please identify yourself and --

DR. MAHOWALD: This is Mary Mahowald, University of Chicago. Could you clarify the -- could you set the stage -- probably Dr. Johnson may wish to speak to this -- of how in the clinic you would deal with a patient whom you typically see for whom, as you acknowledge in your presentation, the standard of care would be colonoscopy, but as your presentation makes clear, some people don't want it for whatever set of reasons. You would be recommending, I assume, standard of care, as any physician would. But the patient would say something like, no, I don't want to do that, or I don't really like that. That's what I would always say, I don't really like that. But would you then recommend because I don't like that that, all right, you could do a blood test, but this test, I admit, is not going to be as helpful in terms of determining your status as the other, but you could do this? I mean, that's one thing that I'm perplexed about.

The other thing I'm perplexed about is at what point -- in a certain sense, it seems to me inappropriate for a physician to recommend -- recommend is the key word here -- a test that is not standard of care to a

particular patient. I mean, this can become so subjective and interchanged in terms of what you as a doctor yourself consider best for the patient. So, are you saying to him or her, all right, this isn't the best, but if you don't want to do this, we have this other test that you can take. I mean, describe that scenario of how you might bring up this possibility to some particular patient, who, like most patients, doesn't really want to do a colonoscopy, having gone through it before.

DR. JOHNSON: Well, thanks for the question. It's probably not the colonoscopy that you didn't want to do. It's the prep, unless that's a secondary issue. But it's real life, which you say, is the way I deal with patients every day, and the clinicians around the table will say we recommend things, and patients say, no, I don't want to have that. Now, we do know that there are ethnic reasons, there are cultural reasons, and there are maybe age variant reasons that patients clearly will not accept one level of testing. It's very clear. There's no question that ethnicity plays into it, cultural reasons play into it, that they won't accept one type of test over another.

Bridging the gap gives options for choice. And the way that we do that is we say if, you know, in my best interest as your patient champion, I say that this is the best test for you, please, this is the recommendation, hopefully that'll broker the deal and conversations will end with I'm trying to do the right thing for you. When that says no, then you have another option.

Well, if you won't accept that, will there be other things that, either culturally or ethnicity-wise preferential? I just can't convince you that doing the best test is the right way to go.

DR. MAHOWALD: But you would try to convince me? In other words, I don't really want to do this wouldn't be enough for you to recommend Epi proColon testing? My just saying I hate this test, I don't want to do that prep again, that's not enough? I'd have to say, no, I will not do it. Is that what you're saying?

DR. JOHNSON: Agreed.

DR. MAHOWALD: Okay.

DR. JOHNSON: It's got to be driven by the patient understanding the evidence. The physician or the care provider is a champion of the evidence, and the best care plan is the one that really delivers the test being done. So we are always in that position of patients saying, you know, this test is great and this test is not so great. But if you're only going to do this, and we're talking about a menu of options drives patient's compliance. And so there is a menu of option out there that clearly isn't getting the gap closed.

DR. NOSTRANT: I want to ask a couple questions. Dave, do we have any data on how primary care doctors are going to attempt or would attempt to use this test and trying to explain the options that are available compared to gastroenterologists? You and I as gastroenterologists would

certainly be very strongly in favor of using the standard of care, but do we have any data -- where most patients are going to get their information is from their primary care doctor. And do we have any information about how that would be utilized?

DR. JOHNSON: I'll defer that to the Sponsors. From the context of primary care, it's -- this was not part of the pivotal study and certainly the follow-up study that we were involved in.

DR. TAAPKEN: Well, if you ask about data, no, we don't have the data yet. Obviously, the product is not out there in use, so that's why we could not have the data available. However, we are addressing this through labeling attempts and educational attempts that we intend to implement once the product is in use.

It is, I think, clear, and I guess Dr. Johnson would concur, that in the primary care setting, many times, the time that a physician has with his patient is not extraordinary long, and he's trying to guide that patient in the screening-eligible age into the right thing to do. And at this point in time, there are not a lot of alternatives available for that patient if he refuses to choose standard of care. So, our goal is really to make sure that patients understand that this should not be the primary choice, but it should be -- before the patient walks out of that office and says, no, and I'm not going to get screened, that he actually chooses to go home and get this test done.

DR. NOSTRANT: Again, the second question, kind of the

corollary to that, do you have any information on how many people prefer blood versus stool? From my impression, I would think that most patients would prefer a simple blood test because we're all used to getting that, but do we have any information on that?

DR. TAAPKEN: There's surveys that have been published that demonstrate, actually, that there is a preference for blood over stool, so that kind of information is available, but that's comparing, again, blood versus stool testing, which is a different story than recommending colonoscopy and saying no. I think that's really the key that we want to make here. It is really so that noninvasive test options, in our eyes, should be actually the second choice to the standard of care, which is colonoscopy.

DR. NOSTRANT: Yeah, my third concern is the one I think is the biggest is that are people going to choose multiple testing if multiple testing is available, meaning that if the patient has a positive test with your product, will they then instead of doing that go to another test, oh, is this really positive, and then look to see if he gets another test that's negative and then say, oh, I don't have a risk here. And that's really the biggest concern in the use of the products in the future is going to be whether or not that you're going to use that multiple testing option if they're available.

DR. TAAPKEN: In the proposed labeling, actually, we are not suggesting that this is a risk stratification test, but really a screening test that should guide the patient into the standard of care setting. So, we would

make clear that a positive test result should indeed lead to a patient actually being deferred to a specialist.

Dr. Johnson?

DR. JOHNSON: Dr. Nostrant, you know, that happens in real life beyond our control, so patients have test positive, and the doctor says you need to repeat the test or you need to have the real test done to confirm this. And we can't control beyond certain characteristics of what's already out there and what already is happening with other tests that patients ask that question all the time. So, it comes down to education, both in the understanding of the provider, this is where you need to go, and very definitive, clear as far as what the Sponsor's proposing. But repeat testing by the same modality or another modality is really not an option.

DR. NOSTRANT: Should one put in labeling that that's the appropriate thing to do or to make that a stronger portion? I know that's probably a little bit too much, but the argument is that's something that probably should be impressed upon the patient as much as we can.

DR. TAAPKEN: That's clearly understood, and that's why we made this proposal in the intended use, that we say that any patient with a positive result should be referred to a diagnostic colonoscopy. We do not refer these patients to additional counseling or additional recommendations or anything. We basically say they should go straight to colonoscopy and see their specialist.

DR. HICKS: I just had a question for Dr. Johnson. You would agree that colonoscopy is both diagnostic and therapeutic, right? So, and say a patient refused that -- her concern -- but in reality, knowing that, for example, they said I would take a barium enema, you know, would you let somebody have that test even though it's got decreased sensitivity and no therapeutic value, would you utilize that in a screening setting as an alternative if the patient said I won't do that?

DR. JOHNSON: That comes down to education of the patient and talking with them in the specifics. We actually removed barium enema from, I think, the most recent iteration of guidelines because it's so poorly done, so few centers are willing do it. But, nonetheless, the best test is the one that ultimately gets done. If we go down on our sensitivity or trade off on our specificity, we ultimately have to weigh it against the person that didn't get any test, and the ultimate loss is the person didn't get screened at all.

DR. PRZYGODZKI: Dr. Skates?

DR. SKATES: Thanks for the presentation. I wanted to follow up on this issue of the closing the gap and the effectiveness of a blood test to increase participation. And what is the -- is there any evidence from either the pivotal or the non-inferiority trial that that actually occurs, or if not, is there any evidence beyond a questionnaire of preference that actually offering a blood test does get to people who wouldn't have taken a test

otherwise? Is there empirical evidence rather than just a preferential evidence?

DR. TAAPKEN: Well, no, at this point, we do not have that data. Again, the pivotal trials were conducted in such a manner that we included screening-eligible patients that it was clear when they enrolled into the trial that they would already be agreeing to both test modalities. So, the real point of choice would have to happen, guided and counseled by a healthcare provider in a real-life setting, we feel, in order to generate data that is meaningful enough to say to what extent that gap closure can be accomplished through the utilization of Epi proColon.

DR. SKATES: I guess the reason I ask it was because that was a huge component of this particular -- of your presentation in saying -- and the rationale for having a blood test there in the first place.

The other question I have is that part of the assertion was that early detection is important here. And is there evidence that you're finding the cancers earlier compared to those that wouldn't take a test? For example, the sensitivity for early stage, Stage 1 cancer, is about 40%. And perhaps that's what happens without screening anyway. So, any evidence that you've got an increase in early detection because of the blood test?

DR. TAAPKEN: Well, I think the key here is that through a test that is performed, you have a possibility to send patients to go and see their physicians for follow-up once -- at a stage when they're still asymptomatic.

But maybe I leave that to Dr. Johnson to tell you what the rates are of patients that come when they're already in symptomatic stages.

DR. JOHNSON: Yeah, I think it's a good question. And, certainly, the more advanced you become in your staging, the more progressive towards Stage 4, the more likely you are to have signs or symptoms. And signs or symptoms meaning bleeding, change in bowel habits, obstructive type factors, weight loss, or signs that you've got anemia, and something that would drive you to a diagnostic test rather than a screening test. So, a screening test that captures early, pre-symptomatic, pre-abnormal test abnormalities certainly gives us an opportunity to create a better chance for a cure.

DR. SKATES: So was there an increase in early stage disease in either of your trials?

DR. JOHNSON: Well, I'll speak to the trial that we had. It was equal across the -- and non-inferiority across all stages as it relates to the Epi proColon and the FIT trial.

DR. SKATES: I meant compared to not having done the test?

DR. JOHNSON: I can't answer that. And I have to defer to the sponsors.

DR. TAAPKEN: If I understand correctly, you want to understand whether there is a difference between the observed distribution of cancers in different stages --

DR. SKATES: And what you found, yes.

DR. TAAPKEN: Maybe we can bring up the slide, please? Slide up. So here we have the data from the two trials where we show the stage distribution of the cancers that we found in these two trials. So, basically, we would, according to the depiction that Dr. Johnson showed in the beginning, say that, you know, all stages, 1 to 3, are actually stages which are relevant to find for reasons of being able to be treated with a relatively high success rate. So here, the combined sensitivities in both trials for these stages 1 to 3 cancers are 64 and 69%, respectively. That's always the last row on these two blocks of data, which basically demonstrates that we are, by and large, able to find two out of three cancers in that early treatable stage.

DR. SKATES: Right. And the question is how does that compare if you don't have the test? What is the fraction of cases that you find in early stage without the test? So does your test actually increase the early stages of cancer?

DR. TAAPKEN: Right. So the only figure that I'm aware of is the 60% number, where 60% of the cancers are actually treated at a point when they come to see their physicians at symptomatic stages, and I'm not sure if Dr. Johnson can confirm that number, that that stems, I think, from ACS or some other public available source. So, it is our view that colorectal cancer goes undetected for a long time. Typically, people develop the disease, don't go see the doctor, and only go there when it's actually too late, and at that

time, obviously, the detection in the clinic is at a later stage.

DR. PRZYGODZKI: Yes, please?

DR. McSHANE: I have a series of questions just to clarify the study designs that are on my mind. So in the -- what you're, I guess, calling the non-inferiority study or the additional clinical study, there seem to be -- the criteria to get in that study, the patient was already -- those who had colorectal cancer had already been coming in to get a colonoscopy as part of basically a diagnostic workup because of, you know, worrisome symptoms, is that correct, as opposed to the first study where it was truly closer to a screening type of situation?

DR. TAAPKEN: Can I have the study design slide for the FIT comparison trial, please?

So, basically, what we -- slide up, please -- so what we did is we had the goal to -- the primary objective of the study was to compare the non-inferiority of Epi proColon to the FIT test, so that was the primary goal. In order to be able to do that on a sufficiently large number of cancers, if we would have collected those cancers in a truly prospective setting, that study would have been over-proportionally large.

So, what we did is we had a group of patients which we referred to as Group B. These are truly screening patients pretty much like they were in the pivotal trial, same inclusion/exclusion criteria. Now, what we did, if you look at Group A, what we did is we added a number of cancer

patients that were identified in a screening setting and in such screening setting were identified as being colorectal cancer patients. So these cancer cases were basically added to the overall study population in order to have a large enough number of cancers to evaluate the non-inferiority of one test to the other.

So, behind these cancer cases, in essence, there have been tens of thousands, or at least many thousands of colonoscopies, routine screening colonoscopies done in order to identify these subjects. So, there was no stratification or any other selection of those patients.

DR. McSHANE: Okay. But then they are different than the ones that were in the prospective trial, the first study, because they came to your attention because they had undergone colonoscopy, and you knew they were positive, and they underwent that colonoscopy either because they were willing to comply with screening recommendations, or maybe they had some symptoms. So would you agree with me that they are somewhat different types of cases than in the pivotal prospective trial?

DR. TAAPKEN: No, they were not symptomatic. These were all asymptomatic average-risk patients going to have the first colonoscopy for screening purposes. That's how this population was generated. And it was just in that screening effort, that once there was a cancer identified, we asked these patients to provide both matched blood and stool samples. So, these patients were not in any other way different. The only difference that

you could point out -- to is that, obviously, we were not able to have those patients that in the context of the colonoscopy underwent curative biopsy. So, if there's any group that was excluded from that, it was exactly that proportion.

But, again, for comparative purposes, this was affecting both tests in a comparison setting. You could argue that you would not jeopardize your result there. And in terms of overall sensitivity and specificity observed in the trial, it was quite comparable with that in the pivotal trial. So, we tend to believe that, although we cannot prove it, that the exclusion from the curative biopsy cases did not affect the study in any meaningful way.

DR. McSHANE: So, to follow up on a point that you just made about any curable, you know, cancers would have been taken out at the colonoscopy. So, I was wondering about your thoughts on whether that would have differentially affected the performance of the FIT test versus your test? So, in my, you know, non-medical mind, I'm thinking, well, okay, you took the sample after the colonoscopy was done and after you'd cleared out things like polyps and maybe early stage, very early stage cancers, and think about how the fecal test might work. You know, you need the stool to be passing through the colon where it would be picking up some of these markers you're looking for. And in the blood test, you're not.

So, if, you know, you look at that specificity of 97% for FIT in that study versus the roughly 80% for the Epi proColon, so do you believe

that a potential explanation for that disparity could be that the fact that you are taking the stool sample after you've done the colonoscopy and that that would have more of an effect and potentially make the specificity look better for the FIT test compared to your test? I mean, it would -- you know, in other words, it would be working against you. And so my follow-up question, then, after you answer that is, are there other data on the FIT test that got comparable specificities to what you saw in your -- what you called non-inferiority study?

DR. TAAPKEN: Yeah. So, what we did also as part of the inclusion criteria was to set a time window of at least 10 days after such colonoscopy has happened before we actually did the collection of the blood and stool specimens in order to avoid any effect that might have arisen during this colonoscopic procedure to be influencing the results both for stool and blood testing.

We made that judgment based on medical recommendation and input, but of course, we do not have data that would be able to -- that we would be able to provide where we could guarantee that there is no residual effect. But I would think that maybe Dr. Johnson can comment on whether or not he believes after 10 days there would be some residual effect observable.

DR. JOHNSON: It's a pretty long time. If I looked at colonoscopy after a biopsy, sometimes even after I take a polyp out, I have to

go back for another reason, the closure of that mucosal defect is fairly quick. So, it would be very unlikely there'd be any kind of mucosal disruption still persistent at the time. I think it depends on the nature of what was done and how things were done, but I think a reasonable time window, it was 10 days or more, so that the time window of procurement here was, I think, long enough for -- again, I'm not -- it wasn't asked in it, but I would be very comfortable with that number.

DR. McSHANE: Okay. Because what I was thinking is if it's the polyp itself, let's say, that's causing the positive that would be regarded as a false positive because it's not cancer, the polyp is no longer there. So it seemed to me that there was at least that potential that you could be getting a lower specificity estimate because some of the reasons for the false positives were removed with regard to the FIT test, but not for your test, that somehow it could be in the bloodstream, you know, but no longer in the colon because it was coming from the polyp that you took out.

DR. TAAPKEN: I mean, the specificity level observed in the FIT comparison study for the FIT test was, I would say, at the higher end of what you would expect from the literature. So, there is, of course, data which varies widely in the literature, so it's very difficult now to make a prediction as to what the normal specificity for this FIT test would have been in a situation where that would not have been the place.

However, since we're talking about the specificity, and I think

that's maybe the critical point, we're looking at those screening-eligible patients that went in and had no biopsy. So we're not talking about the actual cancer group. So, I would not think because these patients delivered specimens before colonoscopy and before blood sampling that there's any effect that would be applicable here.

DR. McSHANE: Okay.

DR. PRZYGODZKI: Thank you. I would like to have -- thank you, Dr. McShane.

Dr. Weck, please?

DR. WECK: Karen Weck, University of North Carolina. I just wanted to take a step back and ask a question about the analytic sensitivity, how the test is actually run, and then I have, you know, some additional discussion about how well the test works clinically to either pick up or rule out colorectal cancer.

But this is a real-time PCR-generated test. And I do note that the way the test is run, the PCR replicates are done in triplicate, and my understanding is that any one of three positive PCR results would be considered a positive test. That's very unusual for a very sensitive PCR-based test that one would do three replicates and call a positive test based on any one out of three.

And I do note that in the Executive Summary given to us by the Sponsor, on page 13, you describe some case control studies that were done

that weren't shown to the audience here, but I do note that the sensitivity of the -- analytic sensitivity of the test in the first study was only 50%, with a specificity of 95%. And then it says through an iterative process with incremental improvements over the course of time, the sensitivity was increased to almost 70% analytically with a concordant decrease in specificity to 90%.

And I'm just wondering if you could describe what was done in this incremental improvement to the test itself to get the sensitivity up to the current 70%, you know, and just describe -- I don't have a good feeling for when this test is run, how often do all three PCR replicates agree positive versus how often is only one of the three replicates positive. It just is, you know, with the potential for false positives and decreased specificity with PCR tests, I'm just a little concerned about the way the test is set up.

DR. TAAPKEN: I'd like to call Dr. Weiss to the podium, please.

DR. WEISS: My name is Gunter Weiss. Quite a couple of questions, and I might re-ask some of them because I couldn't get all of them. One detail on our test, the positive control, which is run as a batch run control from the very beginning, through all -- through the workflow contains methylated Septin9 as a target, and we require that all three replicates of the PCR are positive to validate a run. This concentration is above the LoD limit, certainly, but pretty low in concentration.

I talk about this because this provides to us information how

reliable or how consistent those three PCR replicates are. If we go into the range of the limit of detection, or maybe two-fold, four-fold above this limit of detection, there we see an inconsistent number of PCRs being positive.

DR. WECK: Right. Yeah, that makes sense to me that the lower number of replicates being positive may indicate that the limit of detection is at the limit of detection of the assay, you know, and so that the test may not be sensitive enough to robustly detect all three replicates positive in each sample. But so the question is, in practice, so if I'm running this test in my laboratory or during the clinical trials that you did, how often in the test samples -- I'm not talking about the positive control -- but in the test samples, how often were all three replicates positive versus only one or two?

DR. WEISS: It's the majority, but from top of my head, I would estimate about one-third in those screening trials we did, and that's different than -- to other case control settings.

DR. WECK: And did you see any difference in that depending on the stage of cancer?

DR. WEISS: There is a dependency. So with the clinical sensitivity, which somewhat relates to the stage of the disease as goes along this number of, say, negative or positive PCRs.

DR. WECK: Okay. Thank you.

DR. WEISS: You're welcome.

DR. PRZYGODZKI: Excellent. I have to stop at this point. We

will have additional time to request questions later on.

I would like to request a few-minute break until the top of the hour, and I'd like to note to the Panel to not discuss this subject among yourselves at this point nor with the public. Thank you. We'll be back at 10:00.

(Off the record.)

(On the record.)

DR. PRZYGODZKI: Okay. The meeting is open again, and I'd like to ask the FDA representatives to present their findings. Again, I would like to note to the audience that if you have a burning question, please let me know. Otherwise, please wait until the public commentary is available. Okay. Thank you. Please.

DR. LEE: Thank you. Good morning. My name is Eunice Lee, and I'm a scientific reviewer in the Division of Immunology and Hematology Devices in the Office of In Vitro Diagnostics and Radiological Health. I'm the lead reviewer for this premarket approval application, or PMA, for the Epi proColon from Epigenomics AG for colorectal cancer screening. Today, Dr. Pantoja-Galicia, Dr. Tzou, and I will be summarizing the FDA's review of this PMA.

The review of this PMA submission has involved the work of many individuals from different offices and divisions across the center. Dr. Zhou is the medical officer, and Dr. Pantoja-Galicia is the statistical

reviewer. Other areas that were reviewed include software, the analytical studies, manufacturing, bioresearch monitoring, epidemiology, and patient labeling. The primary reviewers are listed here, but I would also like to acknowledge that the review team extends to the managers as well as to past reviewers who have been involved.

Today, the FDA presentation will be presented in three parts. In the first part, I will provide background for the Epi proColon test. I will discuss the rationale for the Panel meeting and then summarize the regulatory history of this PMA and give a brief description of the device, including the proposed intended use and the device workflow. I will conclude with the analytical studies which were conducted by the Sponsor.

In the second part, Dr. Pantoja-Galicia will present the results from the two clinical studies included in the PMA submission. He will review the study designs and the study results, focusing on the study population, the primary objectives, and the influence of demographic factors on test performance. He will also present the benefits and risks of using Epi proColon.

In the third and final part, Dr. Tzou will discuss key aspects of the clinical studies as they relate to the FDA questions for Panel discussion. He will also present the post-approval study proposed by the applicant along with additional review considerations.

Epi proColon is a first-of-a-kind in vitro diagnostic device. That

is to say that no device for the proposed intended use is currently cleared or approved in the United States. So, based on the test performance of Epi proColon, FDA is seeking Panel input on the safety and effectiveness of this first-of-a-kind device. In addition, we are seeking input on whether the benefits outweigh the risks of using this device in the context of the proposed intended use. So, as we continue through our presentation, please consider the Panel discussion questions that are in your Panel packets.

So, this PMA was initially submitted as a modular PMA such that the contents of a traditional PMA were submitted as well-defined components or modules. The first module was received in December of 2011. With the submission of the final module in January of 2013, the modular PMA was converted to a traditional PMA and assigned PMA number P130001. In February of the same year, the PMA was filed and priority review was granted. A major deficiency letter was issued in April, and a complete response to the letter was received in October.

From the Sponsor presentation, you saw an excerpt from the proposed intended use. The complete proposed intended use for Epi proColon is shown here. It reads as follows:

"Epi proColon test is a qualitative in vitro diagnostic test for the detection of methylated Septin9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the target DNA sequence in the promoter region of the SEPT9_v2 transcript has been associated with the

occurrence of colorectal cancer (CRC). The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin9 DNA target.

"The test is indicated to screen patients for colorectal cancer who are defined as average risk for colorectal cancer by current CRC screening guidelines. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. Men and women 50 to 85 years of age were included in Epi proColon clinical trial. Epi proColon test results, together with the physician's assessment of history, other risk factors, and professional guidelines, may be used to guide patient management.

"Epi proColon test is for use with the Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument."

A number of warnings and limitations have also been proposed by the Sponsor to be included in the product labeling. The proposed warnings are as follows:

First, Epi proColon test is not intended to replace colorectal screening by colonoscopy.

Next, positive test results are not confirmatory evidence of CRC, and therefore, a positive test result should be referred for diagnostic colonoscopy.

Also, negative test results do not guarantee absence of cancer. Patients with negative test results should be advised to continue

participating in a CRC screening program that includes colonoscopy, fecal tests, and/or other recommended screening methods.

Finally, positive results have been observed in patients with chronic gastritis, lung cancer, and in pregnant women.

A few of the proposed limitations are listed here. One of them is that Epi proColon test is an alternative screening method for patients who are defined as average risk for CRC by current screening guidelines and who are unwilling, unable, or do not undergo screening by other recommended screening methods.

Epi proColon has not been evaluated in persons considered to be at higher risk for developing CRC.

Also, there is insufficient evidence to report programmatic sensitivity of Epi proColon test over an established period of time.

And the last one listed here is that CRC screening guideline recommendations vary for persons over age 75. The decision to screen persons over the age of 75 should be made on an individualized basis in consultation with a healthcare provider.

Epi proColon consists of a series of reagents, controls, laboratory equipment, instruments, and software. Current good manufacturing practice documentation for all of these components has been reviewed as part of the PMA. Of note, the primary reagents and controls are provided in three product kits to be sold separately: the Plasma Quick Kit, the

Sensitive PCR Kit, and the Control Kit. Components that are required to run the test, but are not provided, include BD Vacutainer tubes for blood collection, the ABI 7500 Fast Dx Platform for real-time PCR, and the associated sequence detection software for analysis of the PCR data.

Since the Sponsor has reviewed the procedure, or the device workflow, I'll just highlight some key aspects. So, first, whole blood is collected in BD Vacutainer tubes, which, as I mentioned previously, is not provided as part of the kit. Plasma is then prepared within four hours after the blood draw. Plasma preparations slightly deviates from the tube manufacturer's instructions in that instead of one single centrifugation step, two spin steps are specified in the Epi proColon instructions for use.

DNA is then isolated from 3.5 mL of plasma using the Epi proColon Plasma Quick Kit. Subsequently, the DNA is treated with bisulfite solution, which facilitates the differentiation of unmethylated and methylated cytosines. This is achieved because bisulfite treatment converts unmethylated cytosines to uracil through deamination. In contrast, methylated cytosines are protected from bisulfate conversion and remain as cytosines.

So, the next step is PCR amplification and detection. For a given sample, the bisulfite-converted DNA is divided into three duplex real-time PCR reactions using the Epi proColon Sensitive PCR Kit. The Septin9 target region containing methylated cytosines and an internal control region

in the β-actin gene are specifically amplified in a 45-cycle PCR reaction. Once the PCR is complete, the final step is that the results are interpreted manually relative to pre-specified cycle threshold, or Ct values, for each target region, and a qualitative result is reported: positive, negative, or invalid.

Each PCR reaction is deemed valid if the Ct for β-actin is at or below 32.1 cycles. A positive result is reported if at least one valid PCR reaction out of three replicates yields the Ct value for methylated Septin9 below the reaction limit of 45 cycles. A negative result is reported if three valid replicates yield undetermined Ct values for methylated Septin9. And in all other cases, an invalid result is reported.

The analytical performance of Epi proColon was demonstrated with the following nonclinical studies:

Analytical sensitivity was assessed to determine the limit of detection. Analytical specificity included a variety of cross-reactivity studies as well as interference testing. Studies were also conducted to verify the assay cutoff and analysis parameter settings. Reproducibility and precision studies were also performed. Guardbanding and robustness studies evaluated acceptable tolerance ranges for critical parameters and different failure modes. Additional studies included verification of parameters for specimen handling, preparation, and storage, as well as stability studies.

Most studies were generally acceptable, and remaining issues are being addressed interactively. However, given that the analytical studies

should be considered when assessing the performance of the device, I will provide further details for two of the studies: cross-reactivity and reproducibility.

In the cross-reactivity study, the performance of Epi proColon was evaluated in subjects with chronic conditions as well as in subjects with non-CRC cancers. Among the 16 chronic condition categories that were defined, six had more than 10 subjects, and they are listed in the table here. The positive detection rate ranged from 29% for patients with chronic gastritis to 5% in those with type II diabetes. The Sponsor concluded that no category has a positive detection fraction significantly different from the overall proportion of positive results. Further, out of the 16 categories that were evaluated, four with less than 10 subjects had positivity rates greater than those observed in the clinical studies for the non-CRC group, which was approximately 20%. Due to the low sample sizes for these four groups, conclusions cannot be drawn.

For the study in subjects with different types of cancers, limited numbers of subjects were in each cancer category except for three: lung cancer, prostate cancer, and breast cancer. In this study, the positivity rate for subjects with CRC is 86%. It is 54% for patients with lung cancer, 25% in prostate cancer, and 18% in breast cancer. Among the nine different cancer types that were assessed in this study, four categories with less than 10 specimens had positivity rates greater than 30%. Again, conclusions

cannot be drawn from these low sample sizes.

In light of the results from both of the cross-reactivity studies that I have described, the Sponsor has proposed to include a warning in the product labeling stating that positive test results have been observed in clinically diagnosed patients with chronic gastritis and lung cancer and in pregnant women. The Sponsor has not provided data in pregnant women. However, it has been previously reported that pregnant [women] have high levels of methylated Septin9.

Taken together, it is unclear if the proposed warning sufficiently accounts for all of the results from the cross-reactivity studies, but all of the results should be considered when evaluating the performance of Epi proColon.

The other analytical study that I will discuss is reproducibility. In contrast to the cross-reactivity studies, which tested samples from multiple individuals, the reproducibility study evaluates the consistency of the device performance by repeatedly measuring the same samples. The study was performed at three sites with six operators using three reagent lots and three PCR instruments.

To cover the range of results, a total of 14 clinical sample pools were evaluated. Six pools were obtained from CRC subjects. Five pools were diluted CRC samples. And three pools were from self-declared healthy donors. Aliquots of each pool were sent to each testing site such that a total

of 12 repeated measurements were obtained per pool. Variability in the β-actin results were evaluated in all sample pools. However, due to the limited number of Ct values for methylated Septin9 in the healthy pools, variability in Ct values for the methylated Septin9 results was assessed in only the CRC pools.

So, based on the qualitative results, it's expected that the CRC pools would yield positive test results while the healthy pools should result in negative results. The agreement with the expected test result was 98% for all CRC pools and 75% for all healthy pools. This suggests that false positive results will occur 25% of the time if a negative sample is tested multiple times. Therefore, the results from these analytical studies should be considered along with the clinical study results when assessing the performance of Epi proColon.

So, now Dr. Pantoja-Galicia will present the clinical study results.

DR. PANTOJA-GALICIA: Good morning. My name is Norberto Pantoja-Galicia, and I am a statistical reviewer of the Division of Biostatistics. I will be presenting the clinical studies and the statistical analyses that were conducted to evaluate the performance of Epi proColon.

I would like to acknowledge Dr. Gerry Gray and Dr. Gene Pennello from the Division of Biostatistics for their assistance with some of the analyses that will be described today.

Two clinical studies were conducted by the Sponsor. The pivotal study was conducted to evaluate the performance of Epi proColon compared to that of colonoscopy. A second clinical study was conducted upon FDA recommendation to perform a head-to-head comparison to Fecal Immunochemical Test, or FIT. In both studies, colonoscopy was the reference method used to determine disease status. I will describe the pivotal study first, but before I review the results, I will describe the parameters by which subjects were enrolled in a previous clinical study referred to as the PRESEPT study because clinical specimens that were evaluated in the pivotal study were collected under the PRESEPT trial.

Subjects in the PRESEPT study were enrolled from June 2008 until January 2010. Enrollment in the PRESEPT study continued until 50 colorectal cancer subjects had been reached. Whole blood was collected from each subject prior to bowel preparation for colonoscopy. The samples were then processed to plasma, aliquoted, and archived.

As I previously mentioned, the reference method to determine disease status was colonoscopy, and all pathological findings were confirmed by histological analyses. Subjects were classified into four clinical groups: colorectal cancer, or CRC, included Stage 1 to 4 invasive colorectal adenocarcinoma; advanced adenomas, also referred as AA, included adenomatous polyps greater than or equal to 10 mm, adenomas with a villous component or high grade dysplasia, or HGD; small polyps, or SP, were

defined as polyps less than 10 mm and without a villous component, or HGD; and no evidence of disease, also referred as NED.

Prior to the development of the current version of the device, a prospective evaluation of the Septin9 biomarker was conducted using the first generation assay, which was based on two PCR replicates. This evaluation was based on a subset of PRESEPT plasma samples that included all 53 CRC patients and a subset of 1,457 samples from the non-CRC clinical categories. Crude rates for sensitivity and specificity were 50.9% and 91.4%, respectively.

For the pivotal study, randomized sample batches of PRESEPT samples were shipped to one of three independent U.S. laboratories for testing with Epi proColon in 2011. Fifty CRC samples in the academic study were also used in the pivotal study as well as a subset of AA samples.

Eligibility criteria for the PRESEPT study included the following: Subjects were included if they were 50 years of age or older at the time of colonoscopy, blood was drawn prior to colonoscopy, and if it was their first colonoscopy. Subjects were excluded if they have anorectal bleeding within the last six months, have iron deficiency anemia in the last six months, have high risk for CRC.

Since the pivotal study used archived specimens from the PRESEPT study, additional exclusion criteria were considered for eligibility of the plasma samples for the pivotal study. The samples were excluded if there

was gross hemolysis, there were protocol deviations, and if there was insufficient plasma volume.

A total of 7,941 subjects were enrolled in the PRESEPT study. Approximately 75% of the subjects were enrolled at 22 U.S. sites and 25% at 10 German sites. There were 1084 subjects excluded for the following reasons: 22 were withdrawn; 54 failed the inclusion/exclusion criteria; 3 were non-CRC tumors; 516 have inadequate colonoscopy; there were 32 with no tissue; 307 have insufficient sample volume for testing; and 150 samples from non-CRC subjects were used for cutoff verification. In total, 6,857 subjects were available for selection in the pivotal study.

Among these subjects from the PRESEPT study, 50 were CRC, 653 were AA, 2,369 SP, and 3,785 NED. For the pivotal study, all 50 CRC cases were tested. All 653 AAs were tested except for three plasma specimens that were not located for three subjects. A stratified random selection of the SP and NED groups was conducted to match the age distribution of the U.S. 2010 Census. These resulted in 454 SP and 469 NED subjects.

A total of 1,623 subjects were tested. Among these, 79 were excluded for the following reasons: For 3 known CRC subjects, each sample was distributed more than once to sites; 56 subject sample results were excluded due to invalid controls and unavailability of additional plasma; for 20 samples, there were procedural errors in testing or insufficient quantity of material for testing. Consequently, the pivotal study population was

comprised of 1,544 subjects with valid test results.

The pivotal study objectives listed in the study protocol were the following: Epi proColon shall demonstrate sensitivity of 65% and specificity of 85%. Since FDA does not only consider point estimates, the study objectives were interpreted to consider the lower bound of the corresponding 95% confidence interval. Specifically, FDA's interpretation of the study objective is the following: The lower bound of the two-sided 95% confidence interval for sensitivity should be above 65%, and the lower bound of the two-sided 95% confidence interval for specificity should be above 85%.

The results of the pivotal study are presented here. Sensitivity was estimated as 68.2% with a 95% confidence lower bound of 53.4%, which is below the FDA-interpreted goal of 65%. Specificity was estimated as 78.8% with a 95% confidence interval from 76.7 to 80.8%, which is below the goal of 85%.

Alternatively, device performance can also be evaluated through its predictive values. Since the study population was enriched with CRC and AA cases relative to SP and NED cases, adjusted predictive values were weighted according to the prevalence of each disease category that was observed in the PRESEPT study. As listed here, the prevalence for CRC was 0.7%, 9.5% for AA, 34.6% for SP, 55.2 for NED.

The positive predictive value indicates that the probability of CRC among those patients that test positive was only 2.3%. On the other

hand, for those that test negative, the probability of not having CRC was 99.7%. Also, among patients that test negative, the probability of having AA, SP, or NED is, respectively, 9.5, 35.2, and 55%. Each of these is similar to the prevalence of AA, SP, and NED, respectively. This analysis was conducted by FDA and was also provided by the Sponsor upon FDA request.

As a secondary objective, the Sponsor obtained the false positive fraction for each of the non-CRC categories. It can be noted that variation of the false positive fraction by non-CRC group was not significant. Note that in this presentation, the significance level was considered to be 5%. Furthermore, we note that the false positive fraction for the AA group is similar to that for the NED group, at 22%.

Subgroup analyses conducted by the Sponsor and FDA will be presented. However, this should be interpreted with caution since the pivotal study was not designed to evaluate the performance of the test in subgroups. Although none of them was made to adjust for multiplicity, these analyses are useful to consider.

The false positive fraction was evaluated by age group in non-CRC subjects. An increase was observed with increasing age from 16% to 26%, which suggests that specificity of Epi proColon decreases with increasing age.

Given that certain guidelines recommend routine screening for colorectal cancer up to 75 years of age, FDA conducted an additional analysis

by grouping non-CRC subjects according to this age cutoff. The false positive fraction in non-CRC patients who are 75 years old or younger was 20.5%. And the one for non-CRC subjects who are above 75 years of age was 31.2%. The difference between these groups was statistically significant.

For different ethnic categories, the false positive fraction for non-CRC subjects ranged from 18% to 27%. The false positive fractions differ significantly by ethnicity, and an increase was observed in African Americans.

The influence of other factors on the false positive fraction was also assessed. For the non-CRC group, variation of the false positive fraction by gender and site was not significant. CRC sensitivity by site was also reviewed for the CRC group by FDA. The difference in sensitivity between Germany and the U.S. was 25%. Although the difference was large, it was not statistically significant. It can be noted that this study may not have been powered to detect a difference in CRC sensitivity between Germany and the U.S.

Other factors that were evaluated for the CRC group are listed here, such as age and ethnicity. Variation in sensitivity by each of these factors was not statistically significant.

To summarize the results from the pivotal study, the estimated sensitivity was 68.2%, with a 95% confidence lower bound of 53.4%, which is below the FDA-interpreted goal of 65%. The estimated specificity was 78.8%, with a 95% confidence interval from 76.7 to 80.8%, which is below the goal of

85%. For non-CRC subjects, specificity appeared to be significantly affected by age and ethnicity. Also, we know that the performance of the test in subjects who would not participate in screening colonoscopy cannot be determined from this study.

Now I will present the supplemental study, which was conducted upon FDA recommendation to perform a head-to-head comparison of the Epi proColon test to a commercially available Fecal Immunochemical Test, FIT.

As in the pivotal clinical study, subjects were classified into four clinical groups based on colonoscopy results, CRC, AA, SP, and NED. In addition to clinical data, matched blood and stool specimens were collected from each study participant.

Subjects were enrolled in two groups. In Group A, subjects were recruited retrospectively. Patients had CRC at screening colonoscopy. Please note that CRCs affect the sensitivity and not the false positive fraction. Also, collection of blood and stool samples occurred after colonoscopy, which is inconsistent with the intended use of the test. Sample collection prior to colonoscopy would have been consistent with the intended use, as it was done in Group B. Group B subjects were prospectively enrolled and provided blood and stool samples prior to screening colonoscopy. Groups A and B were set up to have target quotas of 100 and 200 subjects.

Subjects included in Group A were between 50 and 84 years of

age at the specimen sampling, had a diagnosis by colonoscopy or strong clinical suspicion of CRC, had colonoscopy within six months before inclusion into the study, and have specimen sample a minimum of 10 days after colonoscopy.

Subjects were excluded if they have curative biopsy during colonoscopy -- note that this may introduce spectrum bias -- have high risk of CRC, had neoadjuvant treatment, history of inflammatory bowel disease, current diagnosis of cancer other than CRC, acute or chronic gastritis, and overt rectal bleeding or bleeding hemorrhoids.

For Group B, subjects were included if they had the same age requirement as in Group A and were able to provide specimen samples prior to bowel preparation. Subjects were excluded if they have high risk of CRC or any of the criteria listed here.

In total, 337 subjects were enrolled in the supplemental study. Thirty-six subjects were excluded due to incomplete data, curative biopsy, not meeting age requirement, invalid Epi proColon test and missing FIT test, neoadjuvant therapy, no colonoscopy, no sample available, and being at a high risk of CRC. Therefore, 301 subjects were available and had plasma samples. However, 11 subjects did not have stool sample available because they were not provided before colonoscopy or they were not tested within the specified time. Consequently, stool samples were available for 290 subjects.

The results in the next few slides are based on 290 plasma and stool samples.

The primary objective was to demonstrate non-inferiority in a clinical performance of Epi proColon compared to FIT. According to the protocol, non-inferiority of Epi proColon in CRC subjects could be demonstrated if the one-sided 95% confidence interval for the difference in sensitivity is below the margin of 10%. Also, Epi proColon would be considered non-inferior to FIT in non-CRC subjects if the one-sided 95% confidence interval for the difference in specificity is below the margin of 20%. Although one-sided 95% confidence intervals were pre-specified in the protocol, two-sided 95% confidence intervals are presented and were provided by the Sponsor at FDA request.

With respect to the non-inferiority margins between Epi proColon and FIT, this study met the pre-specified success criteria for sensitivity. The difference in sensitivity was -4.2%, with a 95% confidence interval from -16.2 to 8.1%, which is below the non-inferiority of 10%. In contrast, the study did not meet the pre-specified success criteria for specificity. The difference in specificity was 16.6%, with a 95% confidence interval from 10.6 to 22.9%, which is above 20%. Please note that this slide has been updated. The revised slide is included in the folder behind the stapled packet.

Another way to compare Epi proColon performance to that of

FIT is with diagnostic likelihood ratios. The likelihood ratio positive was 3.76 for Epi proColon, and it increased to 26.26 for FIT. This increase implies that the positive predictive value is greater with FIT than with Epi proColon for the same prevalence of CRC. The likelihood ratio negative, which is the ratio of the false negative fraction to the true negative fraction, or specificity, is 0.34 for Epi proColon and 0.33 for FIT. Essentially, likelihood ratio negative results are comparable for FIT and Epi proColon, implying that the two tests have comparable negative predictive values for the same prevalence of CRC.

Results from the "Believe the Positive" combination were considered by FDA after the Sponsor pointed out the proportion of CRC patients that were detected with at least one of the two tests. The "Believe the Positive" rule means that if Epi proColon or FIT is positive or both tests are positive, then the subject is classified as CRC. When this combination was considered, the sensitivity increased with statistical significance to 88.7%, as compared to 72.2% for Epi proColon alone. Specificity decreased with statistical significance to 78.8% as compared to 80.8% for Epi proColon alone.

A comparison between Epi proColon and the "Believe the Positive" combination using diagnostic likelihood ratios indicated the following: The positive likelihood ratio increased from 3.76 for Epi proColon to 4.17 for the combination. This increase implied that the positive predictive value was greater with the combination than with Epi proColon for the same prevalence of CRC, although this increase was not statistically significant.

The negative likelihood ratio was 0.34 for Epi proColon, and it decreased to 0.14 when the combination was used. This decrease implied that the negative predictive value was greater with the combination than with Epi proColon with a statistical significance for the same prevalence of CRC.

For CRC and non-CRC subjects, the 2x2 tables comparing the subjects detected by each test are presented in this slide. It can be noted that each test detected some subjects that were not detected with the other. FDA assessed the association between Epi proColon and FIT. No evidence was found that the two tests are not conditionally independent given disease status.

It has been previously described that among the 301 available subjects, all of them had plasma samples, but only 290 have stool samples. An additional analysis to account for the 11 subjects with missing FIT results was conducted by the Sponsor at FDA request by assuming that the test results were missing at random and imputing the missing FIT results. This analysis supported the conclusion that non-inferiority of Epi proColon to FIT was met for sensitivity, but not for specificity. That is, the results of the study were robust to the missing data.

The performance of a screening test can also be assessed in terms of its receiver operating characteristic, ROC, curve. The ROC curve analysis evaluates the ability of a test to discriminate between diseased and non-diseased subjects. The slide depicts hypothetical distributions of test

results for the non-diseased subjects, in black, and the diseased subjects, in pink. On the left are the corresponding distributions of the results. On the right is the ROC space, consisting of the false positive fraction - or 1 minus specificity - on the horizontal axis, and the true positive fraction - or sensitivity - on the vertical axis.

Now, consider a single positivity threshold shown on the left for which all of the patients to the right of the threshold are classified as test positive. This means that all diseased and non-diseased subjects are positive. This corresponds to the point false positive fraction equals 1 and true positive fraction equals 1 in the ROC space.

If a different single positivity threshold is considered, where only 50% of the non-diseased patients are classified as positive and about 95% of the diseased subjects are positive, this corresponds to the point false positive fraction 0.5 and true positive fraction 0.95 in the ROC space.

Therefore, the ROC curve can be obtained as the positivity threshold is moved along the whole range of possible thresholds. The closer the plot is to the point in the left upper corner, the better the overall accuracy of the test. The ROC curve of a non-informative or random test could fall along the identity line.

In this figure, the black dot depicts the true positive fraction and false positive fraction pair based on the pre-specified positivity threshold for FIT. The blue dot is for Epi proColon. Recall that the positivity threshold

for Epi proColon is such that the test is considered positive if at least one of the three PCR replicate wells is positive.

Using the operating points for FIT and Epi proColon, the "Believe the Positive" combination, as previously defined, is shown. Compared to either Epi proColon or FIT alone, the "Believe the Positive" combination showed an increase in sensitivity and a decrease in specificity, with statistical significance.

Additionally, the ROC plots for FIT and Epi proColon were obtained by FDA and are displayed here. The ROC plot for Epi proColon was generated by varying the minimum number of positive wells to yield a positive test result whereas the ROC plot for FIT was obtained by varying the FIT score. The two tests can be compared in terms of the area under the curve, or AUC, which is a global summary measure of test accuracy. The maximum value of AUC is 1. Higher AUC values indicate higher accuracy of the test in a global sense. The AUC was higher for FIT than for Epi proColon, although the difference was not statistically significant.

Based on the ROC plots, if the operating point for FIT was changed too much, [at] the specificity of Epi proColon the sensitivity for FIT would be higher, as indicated by the vertical pink line. Alternatively, if the operating point for FIT was changed too much, [at] the sensitivity of Epi proColon, the specificity for FIT could be higher, as indicated by the horizontal pink line.

Based on the results from the supplemental study, the diagnostic yield of Epi proColon and FIT can be projected to a screening population to assess potential benefits and risks. Let's assume a hypothetical screening population of 100,000 subjects and a CRC prevalence of 0.7%, as observed in the PRESEPT study. In this scenario, 700 subjects with CRC and 99,300 non-CRC subjects can be expected. Using the estimates of sensitivity and specificity observed in the supplemental study, there would be 505 true positive results with Epi proColon and 476 true positive results using FIT. So, Epi proColon can be expected to detect 29 more CRC subjects than the FIT test using this study.

These analyses also project 19,037 false positive results with Epi proColon and 2,573 false positive results with FIT. Consequently, Epi proColon can be expected to detect 16,464 more non-CRC patients that may be referred to colonoscopy. In other words, for each additional true positive result, 571 additional false positives are expected with Epi proColon. In addition, the ratio of false positives to true positives is 37.7 for Epi proColon and 5.4 for FIT.

Using the same scenario, adverse events resulting from a follow-up colonoscopy from a false positive test result can also be projected. If the risk of an adverse event, such as perforation or hemorrhage resulting from a follow-up colonoscopy is assumed to be 0.68%, then 130 adverse events from follow-up colonoscopies can be expected after a false positive

Epi proColon test and 18 adverse events after a false positive result by FIT. In comparison to FIT, 112 additional adverse events are expected from a colonoscopy after a false positive Epi proColon test. So, for each additional true positive result, about four additional adverse events can be expected.

Taken together, results from the supplemental study have demonstrated that the non-inferiority goal was met for sensitivity, but not for specificity. Lower specificity for Epi proColon compared to FIT leads to potential increase in follow-up colonoscopies from false positive results and associated adverse events.

Compared to Epi proColon alone, the "Believe the Positive" combination showed an increase in sensitivity and a decrease in specificity, both of which were statistically significant. Based on diagnostic likelihood ratio analyses, the positive predictive value increased with the "Believe the Positive" combination, although the increase was not statistically significant, and the negative predictive value increased with the "Believe the Positive" combination with statistical significance.

A summary of the results for sensitivity and specificity from the two clinical studies is presented here. For the pivotal study, overall point estimates are presented as well as point estimates by side. For the supplemental study, estimates for each test and for the combination are included.

There was a difference in sensitivity between Germany and the

U.S. in the pivotal study, but it was not statistically significant. Despite the departure from the intended use in the supplemental study, that is, Group A subjects have colonoscopy prior to specimen collection and curative biopsies were excluded, the overall performance of Epi proColon in the supplemental study appeared to be comparable to the overall performance in the pivotal study.

The pivotal and supplemental studies do not assess Epi proColon performance in patients who are unwilling, unable, or do not undergo screening by other recommended screening methods, which is a proposed limitation by the Sponsor.

Now Dr. Tzou will present part three, review considerations.

DR. TZOU: Good morning. My name is Abraham Tzou. I'm a medical officer in the Division of Immunology and Hematology Devices.

This portion of the presentation will cover some FDA review considerations relevant to the Panel Discussion Questions. Selected related background topics will be mentioned accordingly. Points regarding test performance for Discussion Question 1 will be addressed along with the role of Fecal Immunochemical Testing (FIT) comparison and colorectal cancer (CRC) screening participation.

The role of demographics will be the focus for Discussion Question 2.

Then the appropriate scope of claims as well as follow-up will

be brought up with a review of the concept of test independence for Discussion Question 3.

Aspects of longitudinal study design will be covered for Discussion Question 4.

The Sponsor is proposing that their device be used in the average-risk population for non-invasive CRC screening. Studies in average-risk individuals are not applicable for use in settings of heightened clinical concern, including high-risk patients, for example, predisposition due to genetics; diagnostic colonoscopy, for example, patients with symptoms; or surveillance colonoscopy, for example, patients with a personal history of polyps.

Testing of non-invasive samples is different from other screening approaches that may be invasive or rely on visual interpretation. Evaluation of non-invasive screening includes a balance between prompting invasive follow-up evaluation when warranted and avoiding it when appropriate.

FIT is a recommended non-invasive CRC screening modality across different guidelines. Due to different studies reporting a range of FIT performance, a direct head-to-head comparison to a FIT assay with well-documented CRC screening experience in the intended use setting was advised to help assess the performance of a new in vitro diagnostic device, IVD.

In the supplemental clinical study, FIT comparison was performed under conditions different from the intended use. Group A sampling occurred after colonoscopy, possibly altering test performance characteristics, and subjects with curative biopsy were excluded from the study, potentially introducing spectrum bias with a change in the mix of patient cases.

The pivotal and supplemental clinical studies were designed to examine patients of average risk who would participate in screening by colonoscopy. In the pivotal study, it was the first lifetime colonoscopy. Both the pivotal and supplemental clinical studies are consistent with decreased specificity of Epi proColon compared to FIT; in the supplemental clinical study, 80.8% compared to 97.4%. Although it is unclear why the specificity is relatively low, one observation from the analytical studies was 75% agreement for repeated testing of a healthy donor pool. So, negative results are not consistently obtained. The lower specificity leads to the potential for an increase in avoidable negative diagnostic colonoscopies and colonoscopy-related adverse events relative to FIT as a non-invasive screening option.

In the pivotal clinical study, Epi proColon appeared to have comparable positivity rates whether patients had advanced adenoma, 22%, or patients had no evidence of disease, 22%.

Based on the available evidence, FDA seeks Panel feedback whether the proposed intended use is appropriate. Alternative approaches,

such as an adjunctive second-line option after FIT; prominent labeling cautions highlighting relative Epi proColon performance for colorectal cancer and advanced adenoma compared to other screening option, including colonoscopy and FIT; or other Panel suggestions may be options.

According to the Centers for Disease Control and Prevention, CDC, about one-third of the average-risk population remains unscreened. Organized population-based efforts may be needed to facilitate progress for increased CRC screening. Since patients agreed to screening colonoscopy in Epi proColon clinical studies, use in patients who would not participate in screening colonoscopy cannot be determined. Issues not addressed include the extent to which initial CRC screening test participation, adherence to follow-up diagnostic colonoscopy, and diagnostic yield of findings from colonoscopy would be impacted.

One of the Sponsor's proposed limitations for Epi proColon is as an alternative screening method for patients who are defined as average risk for colorectal cancer by current screening guidelines, and who are unwilling, unable, or do not undergo screening by other recommended screening methods.

The pivotal and supplemental studies do not assess Epi proColon performance in this patient population. It is uncertain how offering Epi proColon to those who are unwilling, unable, or do not undergo screening by other recommended screening methods would compare to other

approaches such as organized population-based efforts. Adequate awareness and counseling are important for understanding benefits and risks of screening tests. If patients do not undergo screening by other recommended methods due, in part, to insufficient awareness in counseling, Epi proColon may not be an appropriate alternative.

Proposed as one of multiple limitations, the importance of this concern may not be apparent to patients and physicians. For these discussions, use of the term "patients" is also inclusive for family members or other laypersons involved in caring for patients while use of the term "physicians" is also inclusive for other healthcare providers and professionals. The Agency requests Panel feedback regarding these issues.

The clinical studies were not designed to assess test performance in subgroups, so those analyses should be interpreted with caution. Statistically significant differences in device performance were observed based on demographic factors such as age and ethnicity. For example, specificity decreased with increasing subject age, with specificity of 68.8% for patients over 75. The Sponsor has proposed a limitation mentioning that CRC screening recommendation guidelines vary for persons over the age of 75. The Agency seeks Panel input whether any finding related to patient demographics and performance merits particular consideration in the product labeling, including materials for patients and physicians.

The clinical performance was evaluated through cross-sectional

study. However, test sensitivity from one-time use in a cross-sectional study is distinct from screening program sensitivity achieved through repeated testing assessed in a longitudinal study. Thus, cross-sectional performance should be interpreted accordingly.

A cross-sectional study at one time can provide performance for initial use in patients who have not been previously tested using the device and may be sufficient for patients who are positive the first time and should be referred for diagnostic colonoscopy. However, if the device is approved, patients testing negative would not be expected to undergo colonoscopy. Would repeating device use after negative results detect significant lesions that were not initially positive? When would follow-up testing occur? A longitudinal study may provide evidence that supports additional repeat testing for patients after initial negative results.

One factor underlying this distinction between cross-sectional and longitudinal performance is the independence of test results. A test applied serially can possibly have multiple opportunities to detect a lesion to the extent that results are independent at each use. However, if results are dependent, for example, the lesion does not and will not exhibit a particular molecular alteration, then cumulative sensitivity would not increase for those patients.

In this independent test scenario, each circle represents a sample from a patient with a significant lesion, and red represents a positive

test. Samples from the same eight patients, that is, circles, are shown at three separate time points going from left to right, same patient at top left corner for first, second, third time point. At each time point, half of the patient samples, that is, circles, are positive, that is, red. Four of eight are red at each time point. If testing is repeated in this independent scenario, the initial test detects four of eight patients depicted in the red box. The first repeat test detects two of the four remaining patients. And the second repeat test detects one of the two remaining patients. This would be desirable for screening program sensitivity.

In this dependent test scenario, the green X represents a positive test using a different approach from the previous red scenario. Again, half of the patient samples, that is, circles, are positive, that is, green X, at each time point. So, the one-time cross-sectional test sensitivity is equal to the previous scenario. Four of eight are a green X at each time point. If testing is repeated in the dependent test scenario, the initial test detects four of eight patients depicted in the green oval, but no remaining patients are detected with a first or second repeat test. This would be problematic for screening program sensitivity.

Combining the two scenarios illustrates a consideration of using a different follow-up test to avoid problematic screening program sensitivity associated with repeating a dependent test. For instance, switching from the dependent green X initial test to the different red test for

follow-up would have detected more of the remaining patients. The initial test detects four of eight patients. Switching to a different follow-up test detects two of the four remaining patients and then one of the two remaining patients.

Although these were simplified scenarios to review the concept of test independence, analysis of this supplemental clinical study suggests that use of Epi proColon in combination with FIT provides additional value compared to use of Epi proColon alone. This could be factored into broader consideration of appropriate labeling concerning follow-up test method if a new IVD is approved that may be used in colorectal cancer screening programs.

The cross-sectional clinical studies provide performance in patients tested for the first time with the device. While a patient receiving a positive result should be advised to undergo diagnostic colonoscopy, there is uncertainty regarding appropriate follow-up for a patient receiving a negative result. The frequency based on time interval and the test method of follow-up evaluation can influence screening program sensitivity based on factors such as the degree of test independence and distribution of lesion dwell times.

According to the Sponsor's Executive Summary, the proposed interval of use is annual testing. However, this does not appear to be stated clearly in proposed labeling. The lack of data regarding repeat device

performance in patients previously testing negative may prompt a preference for testing by a different approach that could be more likely to avoid problematic dependent repeat testing. If so, the rationale and course of action for subsequent screening follow-up after negative results, for example, by FIT, should be conveyed clearly to patients and physicians.

FDA seeks Panel input regarding the adequacy of the Sponsor's proposed warning that patients with a negative Epi proColon test result should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests and/or other recommended screening methods.

The Agency also seeks Panel feedback regarding the appropriate scope of product claims. As discussed, there are caveats in extrapolating programmatic performance for CRC screening from cross-sectional data. In the absence of longitudinal performance results from a newly approved device, limiting product claims to one-time screening, as evaluated in the cross-sectional clinical studies, may be an approach to mitigate safety concerns related to program sensitivity.

Current CRC screening guidelines recommend that patients undergo routine screening with repeat testing over time. Thus, longitudinal study conducted to evaluate programmatic performance of the device in relationship to screening interval may support long-term safety and effectiveness by providing information, such as the negative to positive

conversion rate, that is, screening population patients who test negative and then become test-positive; the diagnostic yield, that is, clinical significant findings on colonoscopy after a positive test results; and the predictive values, that is, probability of disease based on test positive or test negative result with repeated use of the device.

The Sponsor is proposing a longitudinal study aimed at determining the programmatic performance of Epi proColon when testing is carried out annually. The study scheme is depicted here. Starting at T_0, subjects testing positive by Epi proColon will be referred for diagnostic colonoscopy. If subjects test negative by Epi proColon, they will be tested again after a year at T_1, with positives going to colonoscopy. Subjects testing negative at T_1 will be tested again after a year at T_2, with positives and negatives recommended to undergo colonoscopy. For all subjects enrolled in the study, CRC-related medical records will be reviewed two years after the last Epi proColon test result.

The following comments in this presentation along with those in the FDA Executive Summary concerning the proposed longitudinal study are based on what the Sponsor submitted to the Agency in preparation for this meeting. Although some aspects were not included in the materials the Sponsor later provided for the Panel, they are examples of study design considerations for discussion.

Proposed study population criteria are: Average-risk

population, according to the United States Preventative Services Task Force, USPSTF, recommendations for CRC screening; representation of each gender, different age groups, and different ethnic backgrounds; no previous history of screening for CRC by colonoscopy; subjects recruited from clinical sites utilizing Epi proColon.

Proposed study hypothesis is that annual screening program with Epi proColon significantly lowers the probability of carrying undetected CRC such that negative predictive value, NPV3, that is, the probability of not having CRC, in individuals who test negative with annual Epi proColon testing for three years is greater than 1 minus CRC prevalence with statistical significance of 0.05.

It appears that study participants would forgo other CRC screening options. Earlier topic of appropriate awareness and counseling to support this decision may be applicable.

Epi proColon programmatic performance for repeat testing could be inferior to other approaches. For example, offering annual FIT testing could provide greater safety for study participants. However, depending on how annual FIT testing is incorporated, it could complicate understanding of the performance of Epi proColon repeat testing when used alone.

The appropriateness of the proposed study hypothesis to support annual testing with Epi proColon is unclear. It is possible that the

NPV3 goal for Epi proColon could be achieved without having comparable performance to other CRC screening options, such as annual FIT. NPV3 for Epi proColon could be largely due to testing at the first time point with minimal contribution from repeat testing. A device that has limited value for repeat testing after working the initial time could achieve the study hypothesis.

A hypothetical illustration of the proposed study hypothesis rearranged as 1 - NPV3 < CRC prevalence is provided. At time point T_0, pretest probability equal to prevalence of disease is depicted on a 0 to 100% scale. The post-test probability based on a negative result is depicted in dark red.

During the T_0 to T_1 follow-up period, there would be an incidence of disease among T_0 test negatives leading to a pre-test probability at time point T_1. At T_1, the pretest probability could be close to the post-test probability based on a negative result. This suggests limited value of the test at T_1. There would be an incidence of disease during the T_1 to T_2 follow-up period leading to a pre-test probability at time point T_2. At T_2, the pre-test probability could be close to the post-test probability based on a negative result equal to 1 minus NPV3. This suggests limited value of the test at time point T_2.

The proposed study hypothesis could be satisfied even though there is questionable value from repeat testing at time points T_1 and T_2.

Dashed red line shows 1 - NPV3 < CRC prevalence. Controlling for incident disease cases and selection for meaningful performance criteria to evaluate study results may be considerations for study design. To understand how screening performance compares to a recommended option such as annual FIT, the percent FIT positive diagnostic yield from colonoscopy, predictive values, and adherence at T_0, T_1, T_2 would provide a better overall understanding.

In summary, the Panel discussion questions relate to various FDA Epi proColon review considerations.

Regarding test performance for use in the general average-risk population, there is lower specificity in comparison with FIT, similar positivity for advanced adenoma and no evidence of disease, along with inconsistent negative results from a healthy donor pool. For use in those not participating in CRC screening, this has not been evaluated, and appropriate support for screening decisions would be important.

Demographic subgroup differences were observed in performance, including decreased specificity with increasing age.

Issues concerning the appropriate scope of claims as well as follow-up arise from the lack of information for repeat testing, including whether results are independent.

Aspects of longitudinal study design include meaningful evaluation and screening option comparison to address long-term safety and

effectiveness for use in colorectal cancer screening programs.

This concludes the FDA presentation. Thank you for your attention.

DR. PRZYGODZKI: I'd like to thank the presenters from FDA. We have about 15 minutes for the Panel to ask the FDA some brief questions.

Please?

MS. DeLUCA: Jo-Ellen DeLuca, Patient Representative. Dr. Tzou, I think you did a marvelous presentation, and I think you pointed out the elephant that's in the room, and that would be how many of the 65% that we claim as having had screening keep that up. Everybody is talking about yearly screening. I'll bet not half of that 65% goes for a yearly screen. No money, no access, they have not enough for a copay even to pay.

So, when we look at the 80% by 2018, and we're at 65% that we claim it now, how much of that 80% are we going to be able to see given all of these tests that you pointed out?

DR. TZOU: That's a great question. I just want to point out some caveats as far as what the numbers are. So the 65%, the CDC number, first, my understanding of the CDC survey is based on adherence to USPS recommended options. So, although there are multiple options, not all are recommended by the United States Preventative Services Task Force. So, whether Epi proColon, if it were to be approved, would be a recommended option and whether it would methodologically count for that, that's more

details.

So, I think the general concern the FDA has is that there is a potential interest in this. How this would influence that, we're not sure exactly. We're not really sure based on the data we have in hand. And that's why we've come to the Panel to say what are the Panel's thoughts based on the data we have, what the Panel makes of that frankly.

So, we're asking you, based on the data we have now and what you can think about it and what your comments are.

DR. NOSTRANT: I'm specifically worried about one point. We consider colonoscopy to be the standard. We would love everyone to do colonoscopy. That would be our goal, at least at this stage, right now. So the whole data that you presented is based really upon a risk -- decreased specificity, which is -- increased colonoscopies, which is the standard of what we want people to do. I'm not sure why we're doing that.

Then the second aspect of that, which I think is really very important, is that adverse event reaction data that you're presenting is clearly not true. It's clearly not true. It's never been true. All gastroenterologists would be out of business if they had 1% risks of those types of complications. We do too many tests for us to do that. Those are things related to therapeutic interventions, taking out advanced adenomas, taking out polyps. They're not related to the mechanical passage of the tube.

So, again, before we start really talking about specificity and

adverse reactions, we really should have the data on therapeutic versus diagnostic. And my impression is the same that Dr. Johnson has, that the incidence of screening complications of perforation and hemorrhage are very, very low and much lower than that 0.68%.

So, my argument is that doing 256 more colonoscopies here for the same sensitivity -- I don't think holds water. So I, at least, would like your comment on that.

DR. TZOU: Okay. Thank you for the question. So, the figure comes from a recently published Rutter paper from 2012. So, my understanding of that paper, you know, there are methodological issues, but they try to survey results based on when patients had colonoscopy and follow up to see what sort of events were using records. And so they did, to my understanding, separate screening from diagnostic. And there was a lower figure. The figure was 0.47, I believe. Now, of course, you can look through the methods and how they did that and discuss that, but they did try to distinguish screening colonoscopy adverse event rate versus diagnostic colonoscopy adverse event rate, and the numbers that came from that were 0.47 and the 0.68.

Now, the other issue as far as the magnitude and severity of what is classified as an adverse event, obviously, I recognize that as well. So it is not the case that 0.47% of screening and 0.68% of diagnostic were all perforations. That's not the case. So, it is a composite of adverse events.

So, of course, there are issues with composites and how to weight those appropriately, so that's -- so, again, we're not directly attributing saying the specificity false positives would lead to all that rate of perforations. We're just saying, based on what has been reported with an aggregate of adverse event profiles, that this has been suggested.

The other comment I would just make related to that paper is they did note that adverse event rates seem to be associated with age. And so we have this general concern about specificity associated with age, whether age is appropriate for screening guidelines. There is some discussion of whether that's appropriate to begin with. And then if you had that profile associated on top of that, whether that, you know, just as a global impression, does that factor into some decision making.

DR. NOSTRANT: In partial defense of those numbers, very few people have actually looked at data 30 to 60 days post-colonoscopy as well, because most of us don't get back feedbacks. If you have a perforation, your patient is likely not going to come back to you, okay? So, therefore, we really don't know that. And we have only one trial that did show an increased rate at 30 days. So, I think there is some risk related to that. But again, these are, again, interventions against advanced -- things that are clinically indicated. We would do them if we saw them without a concern about the risk. So, that would be an argument as well that I'm not terribly worried about the specificity of these exams, I mean, within reason.

But the argument here is that -- to say that this test is not useful because it has an increase -- or a decreased specificity, to me, is not as strong as a decreased sensitivity, because really, that's what we're looking for.

DR. TZOU: Thank you. I don't think necessarily it's an argument that a all or none statement -- it's more just a relative comparison of the performance profile relative to FIT as a option that has extensive experience and just making sure that people understand that and how to take that all together.

DR. NOSTRANT: Is the manufacturer supposed to put that in their labeling? That's, I guess, what the question is.

DR. TZOU: I think the general question FDA seeks from the Panel is does the Panel think the relative performance raises enough concern that it may be appropriate to make this apparent in the device labeling. So, if the Panel thinks, you know, that there is a difference in this profile and that patients, physicians, and laboratorians should be aware of this, then the FDA would take efforts along those lines.

DR. NOSTRANT: Okay.

DR. GALLAGHER: So for a particular person like me who's not a big scientist -- I understand a lot of science, but I'm not a scientist myself, I'm looking at this and seeing that the device description here talks about the plasma being spun in whatever four hours after collection. A lot of what I've

seen here are from samples that are much older than four hours in terms of comparison. Have we looked at -- has the FDA looked at this difference and whether that is presumed to make any difference at all in what we're considering number-wise here?

DR. TZOU: I'll make some general comments, and maybe Dr. Lee will follow. So, of course, we are interested in both processing specimen stability, that is, when you draw the specimen, and how long is the analyte stable during the process before it's tested. And for the cases of these large studies, we are also interested in specimen storage stability since they're often archived and then tested later on. So, we are interested in both of those questions, and I'll have Dr. Lee follow up.

DR. LEE: So, regarding the four hour preparation time period, that was addressed through robustness studies, where samples were prepared within different timeframes - less than four hours, four hours, and then I think it was up to about 24 hours - to ensure that there would be no significant differences at the four hour time period that is specified. And that is also -- will be included in the labeling to be specified, that samples must be prepared within four hours.

DR. PRZYGODZKI: Dr. Skates?

DR. SKATES: I'd like to understand how the goals for the studies were initially set. What were the considerations that were put forward in that initial planning stage? And then this different interpretation

as to whether the sensitivity, which has been pointed out is a vital concern here -- Here, you said the FDA-interpreted goal for sensitivity was not met. And I'd like for you to expand on that.

DR. TZOU: Thank you for the question. So, FDA has engaged the Sponsor with different interactions throughout the development process. I would say the FDA has provided general feedback. The FDA has not necessarily said this is what the expectations have to be. The Sponsor has proposed different options and objectives and plans, and FDA has basically just commented and provided feedback on them.

I think, in general, for this class of devices, it has not necessarily been easy for FDA to say, well, your performance needs to be such and such. What we have said, generally, is that it is important to understand what the performance is and perhaps in relation to other CRC screening options, and one of those options would be annual FIT. And so, I think the Sponsor tried to incorporate that thinking into their design, but that does not mean the Sponsor's proposal and endpoints were necessarily agreed to by FDA or that FDA explicitly stated what they should be.

DR. SKATES: And then on the frequency, the sense I had from the Sponsor was that there was -- this would engage patients who were not going in for colonoscopies, and it would be a blood test, and therefore, they would then presumably get into a pipeline which would lead to a colonoscopy and a definitive evaluation. Given that the frequency recommended for

colonoscopies is once every 10 years, would it not make more sense for this test also to be recommended once every 10 years?

DR. TZOU: So I think the frequency -- so part of it is understanding what the performance profile is. So, I think colonoscopy is recommended on a 10-year basis based on that understanding of sensitivity and specificity. Dr. Johnson mentioned, you know, there are -- it's not a -- I don't quite remember exactly -- it's not a "polished gold," or whatever his term, but it's not a perfect gold standard. So, other frequencies are also recommended, understanding the performance of that device at that time point. If a device has performance more along the lines of like FIT, then a frequency more similar to FIT might be more appropriate. So, I think the performance profile of Epi proColon is not at the level of colonoscopy, and so to recommend something as infrequently as colonoscopy might not be an appropriate starting point.

DR. McSHANE: One specimen question and one statistics question. The specimen question, you had asked about the sample handling, but I think you were also alluding to the storage. If I understood correctly, in the prospective study, these patients and the samples were accrued over like a three-year period, and then the samples were actually assayed at the end in 2011? Is that a correct understanding of that prospective study?

So was there any examination of whether the length of freeze, you know, could have affected the performance of the test, and do we know

if any of those samples had been thawed and refrozen before they were used in your study?

DR. LEE: So, there was a specimen stability study that was performed, and I believe the last time point was up to 52 months. So it did cover the storage period up to the pivotal trial. And based on those results, I think the results were acceptable.

DR. McSHANE: Acceptable, okay.

DR. LEE: And based on the results that were provided, it didn't seem like storage condition adversely affected the test performance.

DR. McSHANE: Okay. And then one other quick question for statistics. You had done an ROC curve using the number of wells that were -- number of the replicates that were positive in the Epi proColon test. Were you provided with the actual Ct values for both the control gene and the methylated gene? And did you attempt any kind of ROC analysis on the Ct values or the delta CT?

DR. PANTOJA-GALICIA: Yes, that ROC curve was also conducted, so it can be shown.

DR. McSHANE: I mean, you could just -- did it look any different?

DR. PANTOJA-GALICIA: There was not much difference. The ROC was pretty much the same, but you can see a finer granularity in the ROC curve.

DR. McSHANE: Okay.

DR. PANTOJA-GALICIA: Okay.

DR. McSHANE: But you didn't lose much, apparently, by throwing out the Cts and just using the positive and negative at the predefined cut points, you're saying?

DR. PANTOJA-GALICIA: Right, yes.

DR. LIPKIN: Thank you. Very nice presentation. Abraham, I had a question, a couple questions. In talking about the adverse events, perhaps this is, you know, just that your delta was not significant, but I just wanted to check. In terms of thinking -- you did this very nice modeling of some of the adverse events estimated from colonoscopy, and in terms of false positive rates, what would be the difference between Epi proColon versus FIT?

My question is about was it is taking into account or is it worth taking into account the issue of missed advanced adenoma, so a certain portion of advanced adenomas will progress to cancer. And perhaps the numbers on that are actually a little, perhaps, you know, more subject to a difference in the literature. But was that taken into account at all?

DR. TZOU: Right. Thank you for the question. So was benefit/risk, you know, alternatively calculated concerning -- you may be thinking of both cancers and advanced adenomas as positives instead. So the best understanding of advanced adenomas would have been if there were a

direct head-to-head performance in the prospective pivotal trial. Unfortunately, that was not obtained. And in the context of the supplemental trial, because of the therapeutic aspects of colonoscopy, the advanced adenoma representation probably was not adequate to properly understand the relative performance of FIT and Epi proColon in that manner.

So, with some of the limitations of the two clinical studies, to be able to really directly compare advanced adenoma detection in the same patient population directly, head-to-head for FIT and Epi proColon, it was not -- we could try to come up with something for that, but I guess that was not the approach we took because it was somewhat limited to do that.

I guess, indirectly, one would say that, well, what was observed was 22% positivity rate for advanced adenoma. What has been reported for FIT for advanced adenoma is maybe similar to that number, depending on, of course, there are different studies and you can -- and you can't compare directly current studies. What one would say is that the positivity rates for things less than, not as advanced, you know, small polyps and no evidence of disease from the combination of the pivotal and supplemental studies was higher for Epi proColon.

So, if you were to just say the relative distribution -- again, this is indirect, it's not direct, and all that -- but you might think that the advanced adenoma detection rate at an absolute sense for Epi proColon and FIT might be relatively similar, whereas the positivity rate for small polyps and no

evidence you might expect to be higher. So that, just as an initial impression, might not really change the assessment that much.

DR. LIPKIN: Okay. Then a second question. Just so I understand, you know, there are two studies that had somewhat, you know, as you've described or as everyone's described, you know, somewhat different patient populations. But in terms of what's sort of the issue before us today, okay, in terms of, you know, really, which is the patient population we're discussing, you know, on the one hand, you know, there is patients who are obviously defined as average risk. You can quibble about, you know, precisely how that's defined, but sort of importantly, the question is are we really talking about in terms of, you know, a device which is used for just that population, or is it only really the subpopulation of that larger population who specifically refuse the other testing modalities? Because, you know, adjusting that population from one where there's multiple options, let's just say, versus one where there may not be any other option, which are we really talking about here?

DR. TZOU: I think that's one of the questions we have presented to the Panel. So, the proposed intended use, indication for use is more average risk. The limitation describes it as more a subset of that population. And so I guess that is for the Panel to provide input for the Agency to consider. Based on the current available evidence for Epi proColon compared to FIT, is Epi proColon in the general average-risk population,

would that be an appropriate indication for use, intended use? Or would it be more appropriate to narrow the scope if the Panel thought that was appropriate based on what the performance currently is?

DR. LIPKIN: So later, if there are questions on the test, you know, effective, you know, is it safe, before then, it will be defined specifically which population we're talking about; is that correct?

DR. TZOU: So, for the purposes of the discussion questions, I think the Agency raised some possible considerations and also solicited other options for the Panel to consider. That's just more discussions like what is the appropriate segment of the population for this test. That's just for discussion purposes.

My understanding for the voting part is that it is as proposed by the Sponsor. So if the Sponsor proposed such -- that would be what you vote on. Now, my understanding of after you vote, you can also give an explanation for your vote. So, you would vote based on this is what is proposed, I vote on that. If you want to explain why your vote may or may not change based on modifications or whatever, that would be an opportunity to express that also.

DR. LIPKIN: Okay. So thank you. So there is a chance for a little commentary?

DR. TZOU: Yeah, so there's discussion prior to the voting, there's voting, and then there's additional comments after voting, as

appropriate.

DR. LIPKIN: Okay. And then my last question just very -- it's a factual question for Dr. Lee. Is this the first -- would this be the first FDA test, or potentially approved test, that uses DNA methylation? Are there any other approved -- sorry, let me turn the question around. Are there any FDA-approved diagnostic tests that use DNA methylation?

DR. LEE: To my knowledge --

DR. LIPKIN: Maybe you don't know?

DR. LEE: To my knowledge, I believe this would be the first --

DR. LIPKIN: Okay.

DR. LEE: -- in vitro diagnostic test that is looking at detecting methylation of DNA.

DR. LIPKIN: Thank you.

DR. PRZYGODZKI: Thank you. I will add one commentary. The objective of our Panel meeting is to have an unbiased discussion. We all understand where we stand with the issues, questions. We have the ability to ask appropriate parties to get as much information as we need, and when the deliberations end and we do the vote, we actually vote on what we understand and what we had proposed. This is exactly what we're looking at. It does decrease the introduction of bias, and that's what's so important in these studies.

With this, I think it's a great point for us to stop. We have right

now 11:36. Let's break for lunch. Come back at 12:36 promptly. Please take your personal possessions. However, FDA will be manning the room itself for protection purposes. We will not be able to reconvene until that time. Thank you.

(Whereupon, a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:36 p.m.)

DR. PRZYGODZKI: Okay. It's 12:36. I'd like to resume the Panel meeting.

This is the time that we have the Public Hearing portion of the meeting. And the public attendees will be given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such a financial relationships. If you

choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PRZYGODZKI: Okay. We have four individuals that have requested to speak. Each person will have five minutes. We ask that you clearly speak into the microphone to allow the transcriptionist to provide an accurate recording of the meeting, and state your name and what you -- what the question -- or issues that you wanted to address.

First person is Kim Ryan, Director of Patient Information Services, Flight -- Fight Colorectal Cancer.

MS. RYAN: Thanks very much. You almost got it right. Fight/flight.

My name is Kim Ryan. I am Director of Patient Information Services for a patient advocacy organization by the name of Fight Colorectal Cancer. So, these comments are provided on behalf of Fight Colorectal Cancer, a nonprofit, nonpartisan advocacy organization that is committed to the fight against both colon and rectal cancer.

Fight Colorectal Cancer is the leading cancer advocacy organization in Washington, D.C., empowering survivors to raise their voices, training advocates around the country and educating lawmakers and pushing them for better policies. We offer support for patients, family members, and caregivers, and we serve as a resource for colorectal cancer advocates, policymakers, medical professionals, and healthcare providers. Additionally,

we do everything we can to both increase and improve research at all stages of development for all stages of cancer.

Fight Colorectal Cancer believes in fully disclosing conflicts of interest. We have worked with and received unrestricted funding from companies who have an interest in existing and novel screening methods for colorectal cancer, including Fuji, Given Imaging, Quest Diagnostics, Exact Sciences, and Epigenomics. None of these companies nor any of our other corporate supporters have influenced our comments on this issue.

So, screening saves lives by finding and removing precancerous polyps and by detecting cancer early, when it's curable. However, 1 in 3 Americans who should be screened are not being screened even though a recent article identified colorectal and cervical cancer screenings as the most impactful cancer screenings.

New data from the American Cancer Society shows that the colorectal cancer incidence rates have dropped 30% in the U.S. in the last 10 years among adults ages 50 years of age and older due to the uptake of screening. The study finds that the largest decrease has occurred in people over the age of 65 in whom the rate of decline has surged, with the decline accelerating from 3.6% in years 2001 to 2008 to 7.2% during the years of 2008 to 2010. Because screening works, over 50 organizations have united in an effort to increase the nation's colorectal cancer screening rate to 80% by the year of 2018.

A popular phrase in CRC screening is the best test is the one that gets used. We need good screening tests. We also need tests and strategies that address patient-reported barriers to compliance, particularly among the 23 million Americans who should be screened and have not been screened.

For example, screening programs rely on access to appropriate care. Rural or underserved patients may not have access to screening colonoscopy. However, they may have access to a stool-based test or a blood-based test. Screening programs also need to take into account patient preference. For example, patients may have comorbidities which would increase the risk of prep and sedation for a standard colonoscopy. People without symptoms may refuse to consider an invasive procedure such as colonoscopy and the prep required. However, they may be willing to proceed with a less invasive test, such as a stool-based test or a blood-based test. In all of these scenarios, if the initial test is positive, the patient and provider would have a significant incentive to schedule a diagnostic colonoscopy.

Ultimately, sensitivity and specificity data are what matter most, along with the interval of testing. We will be listening today as you consider these issues. As you proceed, we urge you to remember what we previously mentioned. The best test is the one that gets used. If a novel test can improve compliance in a non-compliant population, we wonder if you might consider whether a limited indication may help increase compliance in

a very targeted way. This, in fact, has already been done.

For example, there are patients who are unable to complete a screening colonoscopy for a variety of reasons, such as adhesions. A pill camera was recently approved for these patients, which allows patients to simply swallow a camera, and it transmits pictures to a pack, and then it's mailed to a reviewer. If the pill camera results show that an intervention is required, the patient and physician can proceed with a double-balloon colonoscopy, which is a more complex and lengthy procedure than a standard colonoscopy. However, most patients will require no additional follow-up and will proceed with a normal screening program. This option targets resources specifically at the patients who need them.

In that vein, perhaps it's possible to target populations who refuse or don't have access to standard interventions with some of the novel tests that you are considering today. We realize that this is a complex area and are not urging action. Rather, we appreciate the consideration if the idea is appropriate.

In all situations, we urge you to look at the post-plan marketing research. Ultimately, we would like to see Sponsors and payers work together to create a learning healthcare system which generates robust data that will help increase compliance in a way that decreases incidence and mortality. While we realize the FDA and this Panel cannot require such studies, we urge you to think big to ensure that these new tests have the

impact that we're all looking for, which is fewer deaths to colorectal cancer.

On behalf of Fight Colorectal Cancer, we'd like to thank you for your time and for your careful consideration of these issues. Thanks very much.

DR. PRZYGODZKI: Thank you, Ms. Ryan.

Next person is Dr. David Ransohoff, Professor of Medicine, Gastroenterology, and Clinical Professor of Epidemiology, University of North Carolina, Chapel Hill. You have five minutes.

DR. RANSOHOFF: Thank you. How do I get my slides on the screen? By going forward? Good. Thank you. All right.

I will discuss how noninvasive tests are handled and screening guidelines and what that might mean for FDA's deliberations.

My career has focused on screening, including the process to evaluate diagnostic tests and research methodology, the evaluation of colon cancer screening tests, including the ones listed here, screening policy, and the process to make guidelines trustworthy.

My conflicts and relationships include both sponsors, for Exact as a paid consultant until 2002; and since then, an unpaid investigator/author with no financial interests, no consulting salary, research support, equity patents, and so forth; for Epigenomics, no financial interest. My reward for each is to be an investigator on academic validation studies. I speak for neither sponsor today and have discussed preparation for this meeting with

neither, nor have I shared my presentation. For FDA, I am a member of a devices panel, and my reason to speak is to address one of FDA's stated concerns about its deliberations, the role of screening guidelines.

FDA said in the *Federal Register* an indirect test should be used in accordance with screening guidelines. And then in its Executive Summary, FDA noted that guidelines may differ. Some guidelines say colonoscopy is preferred, an invasive or direct test. For these deliberations, then, my brief topics are: How do guidelines differ, especially about indirect or noninvasive tests? And is a direct test as colonoscopy the gold standard, or the best test, a question that came up by two Panelists this morning. If they differ, why do they differ? And then which do we trust? Last, what are the implications of guidelines for FDA's considering indirect tests? Is indirect necessarily weak, not preferred, not the standard of care?

The Executive Summary discusses the two major colon cancer screening guidelines that came out in 2008. How do they differ in what they say? The ACS Multi-Society Task Force, this is GI societies, and ACR, American College of Radiology, while endorsing different modalities, including indirect tests like FOBT, stated that a structural exam is preferred. That was their words, interpreted as colonoscopy is preferred, a direct or invasive test. In contrast, the U.S. Preventive Services Task Force said that any of several programs, including a program of fecal occult blood testing, noninvasive, is acceptable. This difference and the phrase "structural exam

preferred" received very intense notice of physicians in GI and in primary care.

So why is there this difference? And the answer is because the process to make guidelines differed between the two groups. For the ACS Multi-Society Task Force, there were no pre-stated rules of evidence. For the U.S. Preventative Services Task Force, yes, there were.

Here, there was no assessment of outcomes, like benefits versus harms, quantitatively. The U.S. Preventative Services Task Force did an assessment. And, indeed, the Task Force uses an analytic framework that resembles a clinical trial to look at outcomes over here. I know you can't read this, but these are outcomes of benefits and harms that flow downstream from tests that may be done here.

Conflict of interest was not managed by the ACS Multi-Society Task Force. The participants were almost all gastroenterologists and radiologists, possibly vested in colonoscopy -- I'm a gastroenterologist in radiologic procedures -- with no generalist/methodologist. The process was described afterwards as political in print by one of the group's leaders. In contrast, the U.S. Preventative Services Task Force manages conflict using generalists and methodologists to make guidelines.

So, is this guideline and its conclusion about colonoscopy as preferred, as trustworthy as the U.S. Preventative Services Task Force?

The Institute of Medicine's *Clinical Practice Guidelines We Can*

Trust report in 2011 included a case study of these two guidelines here to illustrate deficiencies in the ACS Multi-Society Task Force process. The American Cancer Society later began to develop a less deficient process to develop guidelines, all of which illustrates in the field of guidelines that FDA and others will consider in accordance with not all guidelines are created equal.

I have two last slides if that's okay. This slide shows a quantitative analysis from the U.S. Preventative Services Task Force about why colonoscopy may not be best as standard of care. And the answer is, at any one application, colonoscopy really is best. It's a very important test. It's how we intervene and do things that are useful. So, at any one application, it may be best, but in a program of screening, colonoscopy every 10 years may miss new or rapidly growing lesions, the ones that kill people and that are detected by a less sensitive test and noninvasive test that is applied more frequently.

In conclusion, then, in considering in accordance with guidelines, what if guidelines and their recommendations differ? The U.S. Preventative Services Task Force recommends any of several programs of tests, including noninvasive or indirect, while others may suggest colonoscopy is preferred, but not all guidelines are created equally trustworthy. In conclusion, the U.S. Preventative Services Task Force analysis, quantitative, explicit, and more trustworthy, as judged by the IOM,

for example, has historically supported noninvasive tests in programs. Such tests are not, as a group, second-class citizens, and especially, as they may be improved, are likely to continue to have important roles.

Thank you for letting me speak to you today.

DR. PRZYGODZKI: Thank you, Dr. Ransohoff.

I would like to ask now Dr. Karen Heichman.

DR. HEICHMAN: Thank you very much for giving me the opportunity to speak to you today. My name's Dr. Karen Heichman, and I am at ARUP Laboratories, which is a national reference laboratory centered in Salt Lake City, Utah. I also have an appointment in the Department of Pathology at the University of Utah.

ARUP Laboratories is a large national reference laboratory, and we're a not-for-profit entity of the University of Utah. We've been an independent licensee of the Septin9 biomarker and have independently developed and validated a test for Septin9 that was launched in 2010. Since that time, we've conducted many thousands of tests in our CLIA-certified laboratory.

As an academic institution, we've continued to be interested in the role of Septin9 in colorectal cancer testing, and we've continued to investigate it with an eye toward improving uptake of colorectal cancer testing, both from the perspective of the patient as well as from the perspective of physicians.

We were involved in a collaborative study with University of Utah, Departments of Pathology and Psychology, together with the Huntsman Cancer Institute, and this involved a small study which involved patient focus groups, where we looked at different cohorts of both screened and unscreened individuals representing different racial and ethnic groups. The hypothesis was that patients may prefer new screening methods without perceived barriers, thereby increasing compliance.

The patients were informed of different colon cancer screening methods by a single moderator, a graduate student who was working towards her Ph.D. And she presented information about the new blood-based test based on the Septin9 biomarker as well as information about colonoscopy, sigmoidoscopy, and FOBT. Following the patient focus groups and discussions, there was also a written survey conducted, and those results will be presented in a paper that's been accepted and is impressed in the *American Journal of Health Behavior*.

Just to summarize some of the important findings, about two-thirds of all of the respondents, including both screened and unscreened individuals, ranked the blood-based Septin9 test as first or tied for first. Also, interestingly, of the unscreened respondents, they also had similar preferences for Septin9, the blood-based test, and ranked them first or tied for first. Majority of the individuals surveyed also listed convenience as a positive aspect of the test.

So, based on this small study, we were able to conclude that blood-based testing may increase screening rates in both screened and unscreened individuals.

With regard to physician preferences for the Septin9 test, a physician advisory panel was assembled, which was led both by Dr. Randy Burt, who is a known colorectal cancer expert out of the Huntsman Cancer Institute, and together with individuals from ARUP Laboratories. And the participants included gastroenterologists, gastroenterology oncologists, internists, family practice physicians, and OB/GYN pathologists and some physician representatives of payers.

Comments that were discussed included from the GIs and the GI oncologist that there was a recognition that some cancers are actually missed even in the setting of the best colonoscopies, and that interval cancers do arise, and that there really is a need for alternative or complementary methodologies to address those cancers which are missed, also to address the issue of patient compliance.

The primary care physicians, however, were interested in Septin9, but there was a reluctance to order new tests that had not yet been incorporated into screening guidelines. And so there was a dichotomy between the specialists and the primary care physicians. And the payers, of course, were interested in detecting colorectal cancer earlier before treating them late.

Finally, I just wanted to give you an anecdote of a patient experience, where a 50-year-old woman, an elite athlete, very educated, said that she knew the statistics and that she was healthy and that she felt her risk of perforation was higher than her risk of having cancer. Ultimately, she underwent the Septin9 test, and in a setting of this test, Septin9 was detected. After reviewing performance of the test, she decided to undergo colonoscopy. And she was very happy to find that there was no cancer detected. Her comments, then, were that she didn't really feel the colonoscopy was so bad and that she would have a colonoscopy at the next time.

Finally, I just wanted to say that the gastroenterologist who treated her indicated that he was really glad that she had had the Septin9 test and that she had ultimately undergone colonoscopy testing.

Thank you.

I also was asked to read a letter from Dr. Laura Porter. She is a representative of the Colon Cancer Alliance, and this is not part of my time, but I was just asked to read this while I was here.

"Dear Committee Members, I'm writing regarding your meeting on March 26th, 2014 for the premarket approval application sponsored by Epigenomics, Inc. for the Epi proColon. I am writing as a representative of the Colon Cancer Alliance. I am a Stage 4 colon cancer survivor and the patient advocate medical consultant for the Alliance.

"I was diagnosed in 2003 at the age of 43 during my second year of my pediatric residency. I had two recurrences and have had no evidence of disease for eight years. I represent the Alliance on several national committees through the National Cancer Institute, as well as other recognized institutions.

"Headquartered in Washington, D.C., the Colon Cancer Alliance is the largest national voluntary health agency detected [sic] to the prevention of colorectal cancer while providing empowerment to families facing the challenge of colon cancer. The Alliance was founded in 1999 by 41 individuals who recognized the critical need for an organization solely focused on the unique aspects of colorectal cancer.

"As you know, colorectal cancer is a major health concern, and despite public education efforts, screening rates for colorectal cancer remain low and have recently leveled off. It is a tragedy that this year, nearly 50,000 Americans will die from a medical condition that is largely preventable. Currently, only two-thirds of the at-risk population for colorectal has been screened. The Colon Cancer Alliance utilizes public health strategies to increase screening to prevent colon cancer. Recognizing that this year 140,000 individuals will still be diagnosed with colorectal cancer, the alliance serves as the leading resource for patients and their families, from support services to financial assistance for individuals with the greatest need.

"We know the best test is the one you do and you do correctly.

For most people, that will be colonoscopy every 10 years. But to increase screening rates, we believe that more patient-friendly options could help increase the stagnated screening rates. We are excited about this noninvasive test option being added to the buffet of options. This is a cancer we can do something about. We need more tests that are accurate and that people will actually comply with. The availability of a noninvasive, easy-to-use screening test could have a huge impact on preventing colorectal cancer and reducing the number of related deaths.

"Thank you for your consideration.

"Sincerely, Dr. Laura D. Porter, M.D."

Thank you.

DR. PRZYGODZKI: Thank you, Dr. Heichman.

So, we're at the point where we're -- the audience could request questions, and if you do have a question you'd like to ask, you have three minutes. Please identify yourself and your affiliation and if there are any other conflicts that may be noted.

Are there any questions from the audience?

(No response.)

DR. PRZYGODZKI: It seems that there are no questions from the audience.

Are there any questions from the Panel to the audience or the folks that spoke?

Please, Dr. Skates?

DR. SKATES: This is for Dr. Ransohoff. You indicated that one of the advantages of the other tests besides colonoscopy, over colonoscopy, is the increased frequency with which they could be done, and thereby detecting more cancers, interval cancers in that. That's the positive side of an increased frequency of tests. Do you have any comments about the other side of that coin, which is there's going to be an increased frequency of false positive results?

DR. RANSOHOFF: Yeah. The main comment is that this needs to be looked at in a quantitative way. It's a very important thing. If you have a false positive rate of 10% or 15%, like mammography, you end up getting a biopsy, you know, the cumulative rate after 10 years and so forth is very high. This does need to be looked at quantitatively for any test, and the key features are issues of independence, test independence, and interval, which the FDA presented something about this morning, what the test interval is that people would use or might get recommended, and then what the cumulative false positive rate would be. And in my view, this is the kind of thing that is very well handled in modeling, for example, that the task force will do when you're looking at what are the consequences of one strategy versus another, how many procedures, how many people end up getting colonoscopy, how many people end up with complications. So it's really important, and I think we need a quantitative answer in the absence of

clinical trials which can't be done. Modeling will provide some insights.

DR. SKATES: And just to follow up on that, one of the aspects of the FDA's presentation on repeated tests was the dependence and independence --

DR. RANSOHOFF: Yeah.

DR. SKATES: -- which presumably no one has data on until repeated -- longitudinal trials are done.

DR. RANSOHOFF: Yeah.

DR. SKATES: So that modeling can't supplant those trials in that --

DR. RANSOHOFF: It can't supplant. What -- I'm sorry.

DR. SKATES: -- issue.

DR. RANSOHOFF: Yeah. What modeling can do, it can tell us how important is the uncertainty that we have. The degree of uncertainty is really critical. If some lesions don't bleed, we're not going to find them with occult blood testing. If they don't have mutations or methylation changes and so forth, we're not going to find them with DNA testing. Eventually, we have to learn that, and what we've got to do is figure out how to live with the uncertainty till we do know that. But that kind of question is very, very important. It's life.

DR. PRZYGODZKI: Please.

DR. MAHOWALD: This question is for any of the speakers that

we've had this afternoon, or for that matter, it could go to members of the audience who might be interested in responding.

I was really struck by what I perceived as a difference between the presentations by the Sponsor this morning and the FDA. Maybe I'm missing something, but I felt that the Sponsor's presentation was really emphasizing the idea that this test would even only be used in the situation in which a prospective patient refused to undergo colonoscopy. And yet it seemed to me that in the FDA presentation, part of what I got from it was there could be a recommendation for this being used as a screening test in a much more general way, for people who -- all right, 10 years is a long stretch between colonoscopies -- who might be tested more frequently by the Epi test, and that would be a screen for which the colonoscopy would be recommended earlier than during that 10-year gap.

Now, it was interesting to me that it didn't seem as if the Sponsors were proposing that, but it simultaneous struck me that that would be a valid argument for a screening test that uses this new device. Could somebody respond to what I perceived as a different argument in those two domains?

DR. GATES: From what I can tell, it's the same indications for use both from the FDA and from the Sponsor, and it's pretty clear in the indications for use that it's a screening test for the general population.

DR. PRZYGODZKI: I likewise have that impression as well, but

we have the Sponsor to note.

DR. TAAPKEN: Let me try, if I can, address this question in a rather straightforward and simple way. What we are proposing in our intended use is that a positive test result should immediately lead to a colonoscopy as a follow-up. I think that is clear, and we have no discussion about that, and whether this is a risk or not, that's a different discussion.

Now, the second part of it is what do we do upon a negative test result. And here, indeed, what we are saying is that, in the current situation, we do not have the data to recommend people to go back to do Epi proColon screening every single year for a protracted period of years. What we are saying is that the patient after the test is negative should come back in a year's time, counsel with his physician and get the advice that he would get on day one, which is preferably colonoscopy, and if not colonoscopy, then an alternative noninvasive method of which we hope to be one of them.

So, that's really in essence and simplistically what we are proposing today. We would hope that in a study after approval on the market, in use, we should be able to show benefit of repeated Epi proColon testing as opposed to testing with other methods in year two, three, and four. That is why the proposal that we have made for a post-approval study is to evaluate the benefit of that programmatic use of the assay, which again, I think FDA has rightfully pointed out, we don't have the data to make that claim at this point in time.

DR. PRZYGODZKI: Excellent. Thank you. I want to bring us back to the audience at this point. Does the audience have anything to reflect upon the question that was posited?

(No response.)

DR. PRZYGODZKI: Did anybody in the audience feel that there was a distinction between FDA --

(No response.)

DR. PRZYGODZKI: Is there anybody that would like to make note of that and express in two minutes why?

Please state your name.

MR. RAMAMURTHY: Hi, this is Lakshman Ramamurthy, Director at Avalere Health. I thought the distinction was the intended use abbreviation that was shared by the Sponsor said "for patients who are unwilling to undergo colonoscopy, this should be it," and FDA's presentation said this never was tested in patients who are unwilling to go colonoscopy because they had to go to colonoscopy. That was the difference.

DR. PRZYGODZKI: Thank you. FDA, please?

DR. GALLAGHER: I would like to ask a question of perhaps Dr. Heichman if I could? Oh, I'm sorry. Let him answer first.

DR. TZOU: Abe Tzou, FDA.

DR. PRZYGODZKI: Can I just ask folks -- let's do the Panel portion when we get to that. Maybe that would be best for getting all of

these issues elucidated at that point, because we're bleeding into the audience, and we're also getting Sponsor, FDA interjecting together. And I would like to keep it as pure as possible.

Does the audience have any other issue they would like to bring up or no?

(No response.)

DR. PRZYGODZKI: Okay. Thank you. If not, what I'll do is I will say that the public hearing section of this is now closed.

And now we will move to the Panel Deliberation. And what we will do at this point is we will ask the Sponsors, are you prepared for questions from the Panel, Sponsors?

DR. TAAPKEN: We are prepared, yes.

DR. PRZYGODZKI: Excellent. Panel Members, please ask.

MS. DeLUCA: Jo-Ellen DeLuca, Patient Representative. I read in your notes that the Epi Colon was available in Europe since 2009 and patients are using it; is that correct?

DR. TAAPKEN: That is partly correct. I would like to defer to Dr. Staub to explain the situation in the European market.

DR. STAUB: Uwe Staub. That is correct. We have a Septin9 assay on the market in Europe since 2009, the first version, which has been replaced meanwhile by a second-generation product in 2012, and the product is in use in Europe and some ex-European countries.

MS. DeLUCA: In lieu of colonoscopy or in addition to or supplement to?

DR. STAUB: No, the intended use claim for that product is different. What we say there is will aid in the diagnosis of colorectal cancer. It has no screening claim.

DR. PRZYGODZKI: I have been brought to attention -- I apologize. I'm new at this position. I understand that both Sponsor and FDA are supposed to be questioned at this point for relevance of issues that the Panel has. So, please, I think you were next.

DR. LIPKIN: Thank you. So we're allowed to ask questions of both FDA and the Sponsor, right?

DR. PRZYGODZKI: Yes.

DR. LIPKIN: Okay. I had a question for the Sponsor. Not to be -- okay, yes.

DR. TAAPKEN: It was the computer, sorry.

DR. LIPKIN: Can I ask the Sponsor a question?

DR. TAAPKEN: Sure.

DR. LIPKIN: All right. Thanks. Not to beat a dead horse, but so your proposal in the United States is the intended patient population, okay, up front, all right, is what? Is patients who don't want -- who say I don't want to have FIT, I don't want to have colonoscopy, or every person who's over 50 in the United States who is eligible, or some middle ground?

DR. TAAPKEN: Well, the intended use population is indeed the average-risk population as defined per guidelines in the United States. So this is everybody over the age of 50 which is a no-risk patient that --

DR. LIPKIN: Right.

DR. TAAPKEN: Or non-elevated risk patient, average-risk patient. However, what we are saying in the limitations section is that our special focus is to those patients who are refusing other screening methods as per guidelines today. The reason we cannot make that claim as a main claim for use in that population is that fact that it is just simply not possible to do the trial where you ask a patient to -- ask him if he's willing to do a colonoscopy, he says no, and then you ask him do the comparative trial between a noninvasive test and a colonoscopy. So, that data cannot be generated.

So, what we have done when we have done the study collection is we are of the opinion that the population that we trialed in our trials was indeed quite closely aligned with the unwilling/unable, and one of the reasons for that is the fact that these patients had an average age of over 60 years at the time when they went into the first colonoscopy. So in that sense, as Dr. Johnson said this morning, these patients have been basically colonoscopy refusers or screening refusers for 10 years before they went into this trial. So, that shows that this is actually the population that was, I wouldn't say predominantly, but to a large extent trialed in our pivotal trial.

DR. LIPKIN: But you did do a trial where you, I mean, essentially it was a comparison of the FIT versus Epi proColon, right? That was your second trial?

DR. TAAPKEN: That is the supplemental trial with it, but that was a trial where we compared Epi proColon --

DR. LIPKIN: Right.

DR. TAAPKEN: -- to colonoscopy and FIT to colonoscopy.

DR. LIPKIN: Okay.

DR. SKATES: Much of the discussion in terms of the effectiveness of Epi proColon has been on the sensitivity side and picking up cancers that wouldn't have been detected either because another test wasn't going to be done or because it could be done more frequently than colonoscopy. And you met the target of sensitivity, at least by your definition.

The area that I'm concerned with, and I'd like to hear your thoughts on, is the specificity, the false positives. What would you consider in retrospect to be a safe level of specificity and why? And that's the other side of any screening test. There's always a positive side on sensitivity and a negative side on specificity. Thanks.

DR. TAAPKEN: Well, we never had in the current setting of utilization of noninvasive screening assays, never had a real problem on the specificity side with respect to fear of, you know, putting patients at risk,

because we knew in the reflex situation, once a test result is positive -- which might be unlike other screening settings. Here, the reflex is actually a guideline-recommended colonoscopy. Of course, the question is more what makes sense. And we believe that, you know, the mid-80% range that we set ourselves as a target was a sensible and reasonable target based on what we had seen before in preliminary investigations. And that's why we set that target.

When we came out with the result as we have generated it, we were of the opinion after conducting an internal risk/benefit analysis with input from medical advisors that even with these specific characteristics, the test would have use across all study populations investigated.

DR. SKATES: So can you elaborate on that? What is the risk in the risk/benefit tradeoff? It seems to me that you're trying to assert that there is no risk and, therefore, pretty much any specificity would be acceptable since the follow-up is a colonoscopy, which is recommended anyway. And at some point, with too many false positives, I get nervous in a screening test. And I'd like to understand what that risk was in that risk/benefit tradeoff.

DR. TAAPKEN: Well, if you would consider any risk in that setting, I think it would be the risk of a repeated colonoscopy. After a positive result, you go have a colonoscopy, and rather than just being in the context of being managed by a specialist in that field and adhere to the

guideline of going back to colonoscopy 10 years later, or depending on the finding of the colonoscopy, that you would come back and then just be tested again, go another -- to do another colonoscopy, and so on. So, that is certainly one of the points that we considered to a certain extent to be, you know, if at all a risk.

But the assumption has been, also, based on medical input, that once that situation happens and the patient is in the care of a gastroenterologist, for example, that that risk is indeed a very limited one, because in that setting, the gastroenterology would issue the right recommendation for the patient. And the benefit, because you asked about the risk/benefit analysis, the benefit is indeed what we had discussed before. And based on that equation, we decided that the goal, although we had not met the formal acceptance criteria in the trial, was still sufficient to justify the further development and bringing forward the product.

DR. SKATES: So there's no lower bound on specificity, then? You would accept pretty much any specificity? And the reason I ask this is because one of Dr. Ransohoff's comments, for example, was to quantify that tradeoff between sensitivity and specificity. So I'm looking for quantitative answers, what's reasonable, what's acceptable for specificity in terms of a first-line colon cancer screening test.

DR. TAAPKEN: Again, we have a very hard time to quantify that risk based on what I just said earlier. It would be a totally different story if

you would really, as a reflex to this test, suggest something that is outside of the current screening guidelines. So, we are basically referring screening test result patient to another recommended screening test. So, we're just shifting, basically, a patient from one paradigm to the other. We are not actually doing something that in any way would be a further step that turns out to be unnecessary. And I think Dr. Johnson tried to elucidate, elaborate on this this morning. Maybe he wants to comment on that again.

DR. JOHNSON: Sure. I think the answer is, from my standpoint, is I don't want to miss a cancer. So if I'm going to have a variability, it's not going to be traded off in the sensitivity. So if I get a patient in that's not going to be screened otherwise, I want to have it really complete that I'm not going to trade off sensitivity. If the specificity defaults to no cancer, but there are other variable benefits, that's even a benefit beyond today's discussion. But certainly when you get 40 to 50% precancerous lesions detected, there is another reason to say I can accept that as a relative risk, because that patient should have been that way to begin with.

DR. SKATES: And so you would, again, accept any specificity pretty much?

DR. JOHNSON: Well, I think that the point, again, is anything that gets the patient in is the way to go. Specificity almost, to my standpoint beyond today's discussion, becomes almost a healthcare economics discussion, because it's really driving ancillary use of tests. If you declare that

truly a false positive, it's false positive in that there wasn't a cancer. If you looked at positivity in a true perspective of clinical impact, there may be a lot more beyond just no cancer.

DR. SKATES: So in terms of -- just to get -- so you don't think that there is any downside, for example, false positives, people without colon cancer getting told they may have -- they have a positive test and you need to colonoscopy, the anxiety that creates is really more a motivation in your eyes or that anxiety is not a negative?

DR. JOHNSON: Again, it gets them to a test that we really would prioritize to begin with. There are clearly emotional issues and direct and indirect costs attributable to any ancillary test, and I think that we're very sensitive to that for what drives patient anxiety and behavior. It would be nonsensical to accept that as no cost. The relative value on it, though, is where I'm playing my weight in --

DR. SKATES: So --

DR. JOHNSON: -- I want to make clinical value, so if I do a test that's an x-ray, and I send a patient to another x-ray, there's an anxiety associated with that. There's anxiety associated with screening tests of any time. If you've ever been -- I'm sure you've been a patient, as everybody in the room has been. Anytime you do something, if you're not anxious about it, you're really not paying attention, from my perspective of being a patient.

DR. PRZYGODZKI: Thank you.

Dr. Hicks?

DR. HICKS: Yes. First of all, I want to come back to Dr. Johnson in just a minute, but I had a question for Dr. McShane or Dr. Skates. They can both jump on this. But from a statistical analysis, when you look in the sensitivity study goals that are set and the fact that in these -- the FDA-interpreted goals were not met, where does that kind of shake out clinically? How do you all view that?

DR. McSHANE: I think it's a good question. I guess the reason for having a pre-specified boundary is that we want to avoid a situation where there are multiple analyses to the data until you get something that meets that mark, and that was clearly not done here. You know, they had that pre-specified and had the plan, and they presented the data the way they were.

What is the difference from a practical point of view between, say, a 68% sensitivity and a 70% sensitivity, that I think gets into all the questions that have just been raised here. So what are the downsides of having that additional, you know, 2% that you might miss. And so it's not really a statistical thing.

I guess one thing I'm curious about is really more the representativeness of the patient populations in the studies, and this has been raised already that, you know, we're sort of thinking that -- we have high hopes that this is going to get some of the people who would not have

gone in for colonoscopy to do something. And we heard figures like, you know, a third of the people do not follow the recommendations to go get colonoscopy screening. I'm a little curious as to whether those 30-some percent of the people are the ones who don't even go to the doctor and aren't going to be in the doctor's office for the doc to check off, yes, get this test or get, you know, the FIT test. So, I would be interested in anyone's comments on whether they have some better data on that.

And I think we're in an unusual situation here with regard to the false positives, as Dr. Skates has been sort of going back and forth with the Sponsors on this, that what's unusual is that what we reflex to, if the person comes up positive on this, knowing that there might be a 20% false positive rate is what's recommended in the first place. It's not as though we're sending them off to get some new diagnostic procedure that they would not normally have ever gotten. So that makes the decision, I think, very, very difficult.

I guess I wish that we had some better data in the second study that you did that had, you know, that showed the false positive rate for the FIT test being miniscule -- I guess I'm a little skeptical of that -- which would actually sway one in favor of, you know, your test possibly, thinking that, well, it can't really be that good and there must be some biases in that population. So, that's why I asked the Sponsor earlier in the day about whether there were other figures of that type on the FIT test. So, for

example, when the FIT test was approved, what were the numbers that were presented for the false positive rate? And I don't think you really knew the answer to that. I don't know if anybody knows the answer to that in the room, but I would be real curious about that.

So I guess, you know, the bottom line answer to your question is the statistics don't bother me from the point of view of whether it was 68% or 70%. What really bothers me is trying to figure out how I balance all of these other issues and what the real risks and benefits are and the fact that we ran the studies in the patient populations which are not really the ones that we're targeting with this test.

DR. HICKS: With Dr. Skates, real quick, if I could follow up on that. So, from a statistician's point of view, you perceive that the data presented, that the Epi and the FIT both have similar sensitivities reported?

DR. SKATES: Yes, that's correct.

DR. HICKS: Okay. But the specificity is off 20%?

DR. SKATES: There's a, yeah, 15% difference in the specificities, which translates to seven times as many false positives as the FIT test. And, in fact, that was a issue I want the FDA to address because where -- here -- or at least my understanding of the mandate is whether it's safe and effective, but there's -- the question of how does it compare to an existing test is orthogonal to that. And so I wanted to understand why they requested that comparison to an existing test, because it seems to be orthogonal to the safe

and effectiveness. And whether this issue of seven times as many false positives weighed into their considerations in their presentation.

So, I'd very much like to understand -- that clearly seemed to be an issue with the FDA, and I'd like to understand how it relates to the safety and effectiveness.

DR. PRZYGODZKI: Would the FDA representative like to address that?

DR. TZOU: Thank you. Abe Tzou, FDA. So, I guess this circles somewhat back to, you know, the discussion of how was the protocol designed and all, thinking about how to evaluate this product. So, part of the thinking is evaluating the proper context in the landscape of colorectal cancer screening options. So, part of the thinking was how does the performance compare to FIT. And that helps -- so some of the relative questions are to decide what sort of claim is appropriate given the understanding of the tradeoffs in that performance, right? So when we were discussing performance goals, one of the general ideas is, well, how does it compare to all other noninvasive CRC screening options as a way to guide the design of performance goals. And then when that pivotal results were obtained, then that also was prompted to say, well, maybe a direct head-to-head comparison would be more helpful to clarify this understanding of the performance profile. And that could inform Panel Deliberations as to the appropriate scope of claims and the appropriate target population for the

product, to help inform that.

As to your earlier question about, you know, tradeoffs of sensitivity and specificity, I guess you've heard some difficulty from the Sponsor as to how to properly frame the cost of specificity. So I guess one way something to consider -- you know, of course, it's up to the Panel to decide -- you know, on the one there is, starting off, everyone goes to colonoscopy. That's just start off with the up-front, invasive, all-comers strategy. Different strategies would be start off with all comers, to the extent they adhere and comply, but with a noninvasive strategy. And as you heard from Dr. Ransohoff, there are different interval and frequency patterns as to how that actually meets out in the population.

So, if you look at it just from a noninvasive screening option profile, then the risk/benefit profile gives you some sense as to the marginal tradeoff of true positive and false positives. So, as you recall from the pivotal study, the negative predictive value is something like 99.7. So, if you start off with a noninvasive strategy where you are thinking, your expectation is that, well, if people have negatives at a 1 to 300 rate, that's the kind of rate where you would think colonoscopy -- if you're starting off with a noninvasive strategy, you're kind of comfortable with saying that's the rate at which I would no longer want to do colonoscopy. Perhaps. I'm not saying that's necessarily true. I'm saying that's one possible way to start thinking about it.

So, if you look at the marginal tradeoff in this supplemental

study, understanding there are caveats because, methodologically, it was collected post-colonoscopy and all these things, so we recognize those and put that aside, and then the differences in sensitivity are not statistical significant. But the estimate on that risk/benefit profile was something like 1 to 571. So, the marginal tradeoff there, assuming that the point estimates hold and all those caveats, all those things, you know, you have to take all that with a grain of salt, is that the tradeoff is below the negative predictive value at which you were comfortable saying these patients would be deferred from colonoscopy to begin with.

So, although I appreciate Dr. Johnson in his view that, you know, sensitivity is very important and we want to encourage all those people from the view of people who are not getting screened, I guess from the perspective of a noninvasive screening strategy, if you're comfortable with an NPV of a noninvasive strategy on the order of 1 in 300, something like that, for NPV, and your marginal tradeoff is below that, then you're saying that, well, really, I don't want to start off with a noninvasive -- I'm just not comfortable with a noninvasive screening strategy.

So, that's just one possible -- I understand this is still relative, this is not an absolute way to quantify risk, perhaps, as you would like, Dr. Skates, but that's just one possible approach, to at least have some gauge of thinking, well, if I go with an all-comers invasive approach or an all-comers noninvasive approach, what are the relative merits of the expectations, and

where does this marginal tradeoff fit in?

DR. SKATES: And how does that affect the safety and effectiveness criteria with which FDA is charged with evaluating tests? I mean, it seems to me that those are orthogonal issues.

DR. TZOU: Sure.

DR. SKATES: But please correct me.

DR. TZOU: Sure. So, I think the general things the Panel could consider is, you know, what is the safety and effectiveness just for the device as an option in itself, to be an option. I guess the other question would be what is the safety and effectiveness of the device to be where its relative ranking, perhaps, of an option is. Okay. So, it's one thing to be on the menu, so to speak. It's another thing to be a preferred option on the menu.

DR. SKATES: But are you allowed to use this relative ranking as a surrogate or some influence on your judgment about safety and effectiveness? That's the disconnect here. I thought the evaluation essentially is standalone.

DR. TZOU: So --

DR. SKATES: And if it's not, I'd like to understand how to -- if there is some comparative assessment that weighs on the safety and effectiveness, I'd like to understand that.

DR. TZOU: So, I guess it's tied into the proposed intended use and indications for use. So, does it stand alone in the Panel's judgment for

the proposed intended use and indications for use? So, if the proposed intended use and indications for use is the general average-risk, is it safe for this performance profile for that? If the Panel could make a certain decision based on just how that is, they could decide that the relative performance is not a decision for that. Or they could say maybe it does make a decision -- does make an impact. Or the Panel could consider, well, maybe if we consider an alternative intended use and indications for use, then that might change the decision somewhat. So, it is standalone for the performance as we have in hand. Whether it stands sufficiently for safety and effectiveness may depend on what the appropriate intended use and indications for use is.

I'm sorry I'm not directly -- but, still, those are just possible -- I know they're kind of marginal decisions, but --

DR. PRZYGODZKI: Thank you.

Dr. Bujold?

DR. BUJOLD: I have a couple of comments, one for Dr. McShane. In the primary care arena, we're moving into the area of population disease management. And just to use my own practice, once we had systems in place that could measure things like absent care for colonoscopies, we were much more able to identify and then increase rates of colonoscopies in a given practice. So two years ago, our rates in my practice for screening colonoscopies was 30 to 33%. And I just happened to check it last night, and we're up to 75%. It has a lot to do with having the

ability to manage a disease in a population.

And what I have found, if you can actually identify the gaps in care, it's a lot easier to convince people to have things like colonoscopies, you know, once you go through the process of explaining why it's important and, you know, the devastating consequences, et cetera. So, I think you're going to see, as we have the systems in place, you're going to see the rates of screening go up considerably.

And then the second comment was a question for both the Sponsor and the FDA. So people are going to come to us as primary care physicians that, say, don't want to have colonoscopies, and we're going to say, well, you have possibly two options now. One's the fecal occult blood testing, and the other is this DNA-based test. And they're going to come back to us and say, well, which one is the better test and which one is going to cost the most, and which one, based on the data, would you recommend?

So could Sponsor and Panel speak to those issues?

No?

DR. PRZYGODZKI: It's a difficult arena, because we're really evaluating right now the utility, the safety and effectiveness and study itself rather than cost. We should not be really focusing on cost immediately at this point. It could be an effect --

DR. BUJOLD: Well, I'll take the cost question out of it, but the other -- you know, what's the advantage of either, and which one would you

choose based on the data --

DR. PRZYGODZKI: Sponsor speak --

DR. TAAPKEN: Slide up, please. Slide up. Oh, okay. Well, as I was trying to explain before, the situation we're facing is exactly the one that you're describing. The patient walks in into primary healthcare setting, wants to be counseled, is in the screening-eligible age, and might have refused to take a colonoscopy. So, in that setting, it is our proposal that having shown non-inferiority in the ability to detect colorectal cancer, both an FIT test, especially the one that we analyzed, and our test would have similar performance in the detection rate of colorectal cancer.

So, in that sense, the reassurance of a patient based on a negative test result to be free of the disease is equally high based on likelihood ratios or negative predictive values for both of these tests.

So, the only caveat that the physician would have to make is that he would have to tell the patient that in case of a positive result, the consequence would be -- either test, and it's always the same -- to be referred to colonoscopy. And we feel that the rate at which patients would be referred to colonoscopy is not in any way from the medical point of view alarming.

So, when the physician gets the result back from the laboratory at the end of the testing cycle, he will have another opportunity to discuss the results of this test with his patient. And we are absolutely assertive that

we need to send that patient to do the safest thing that there is available, because a positive result of either noninvasive test is an alarming signal that needs to be followed up.

DR. PRZYGODZKI: Dr. Weck? And please question specifically to either FDA or the Sponsor.

Dr. Weck?

DR. WECK: Well, I don't have a specific question, so I may wait until later.

DR. PRZYGODZKI: Excellent.

Ms. DeLuca?

MS. DeLUCA: If I'm reading it right, Dr. Johnson had said something that interested me. It was that what you're really doing is leveraging the technology to improve accruals for screening, and as the patient, that's what we need. I mean, I spend my lifetime moving people to doctor's offices, and it's hard. But is that how -- my take-away from you, Dr. Johnson? Is that what it is -- that the technology you're trying to leverage it into accruing to screenings so that we have more people getting screened?

DR. JOHNSON: Exactly. It's about to your point, what is that third -- the demographics of the third. When people have looked at this, there's structural issues, there are insurance issues, there's access issues, but there clearly are cultural and ethnic issues, too, and patient behavior that we still don't quite understand. But what we do understand is we've plateaued.

And we've done that in colonoscopy. And we're just not getting -- and you're doing great on your 75%. I wish you were my primary care referring doctors. But that's just -- that's an aberrancy, unfortunately, in the continental United States.

DR. PRZYGODZKI: Dr. Nostrant?

DR. NOSTRANT: I guess I asked one question of our European group here. You have five years of experience now with using this test. Have you seen a change in the utility of colonoscopy? Have you seen more colonoscopies? Have you seen less colonoscopies? Have you seen any -- what's your false positive rate? Do you have any data on that from five years of experience?

DR. TAAPKEN: Yeah, as Dr. Staub was explaining earlier, the situation in Europe is that we had a first-generation version of the product that was differently configurated for a different intended use on the market until 2012. And in 2012, we introduced a test that is somewhat comparable, not quite the same, than it is here in front of you today.

Now, we are, in Europe, currently not marketing the test very actively. We have a situation in Europe where every single country has different guidelines, different recommendations for screening, different programs, some of them state-run, some otherwise, so that we have decided, as the small company that we are, that we'll not take an endeavor into branching out into all different countries trying to conquer them all

independently.

So, what we are seeing, in fact, is the situation where, in the markets in which we are active, people are using this test indeed to drive more people into screening programs. So at least the anecdotal we have -- we have not any solid data that we could report here today -- indicates and suggests that these patients that first get tested understand that this is a benefit to be tested, and we have anecdotal evidence as well, which I will not dwell on too much, but at least initial figures that we have seen is that a very high proportion of those who have been tested positive have actually gone on to get a colonoscopy.

DR. PRZYGODZKI: I'd like to ask one quick question, or actually two, if possible. One of them is I noticed that you have 45 cycles for your amplification. I recall that once one crosses 35 cycles, approaches 40, the noise begins to get amplified. How have you folks addressed this issue of the noise amplification of a pretty labile area, which is methylation with bisulfite, and all the other constraints that you have to look at to actually get that true signal?

DR. TAAPKEN: I'd like to defer the question to Dr. Staub. Oh, Dr. Weiss, sorry.

DR. WEISS: Dr. Weiss is my name. So you're right. Beyond 35, things get noisy, but still there are signals. And that's why this test is designed to be a qualitative test. And that's why we count PCR results and

take them seriously, but not really take them as a quantitative measure.

We have run during our development that PCR up to 50 cycles, and in the very late times, up to 55 cycles, depending on certain primer concentration levels, PCRs behave somewhat different, different devices, and so forth. But what we've done for this device is providing us with the certainty that beyond 45, there is nothing to observe anymore. There are nothing showing up beyond that cycle, the threshold level. But in the range, I would say, up to 35, we are sort of quantitative also in the Septin9. Beyond that, it gets more noisy, but still it's reproducible. And then in the very late ones, say, around 40-ish, 38, 40-ish, it's not quantitative anymore.

That does not refer to the β-actin. It's a much more stable one, comes much more earlier. We are there in the range of Ct 30.

DR. PRZYGODZKI: Right. So having said that, when you look at the pivotal trial versus the second trial, I'd like to have an understanding of what major assay differences, even global scope -- were there different primer sets that you were using? Were there different amplification scales that you used? Was there some touch-down PCR, something to that nature that you actually got a better sensitivity and, you know, a greater -- a sensitivity -- more specificity, but you know, greater sensitivity, but lesser specificity through that process? I mean, I'm trying to connect where, from the pivotal to the second trial, where the differences actually were introduced and what possible technique?

DR. WEISS: Are you referring to the first trial as our pivotal trial and the --

DR. PRZYGODZKI: Yes.

DR. WEISS: -- and the second trial being the non-inferiority trial compared to FIT?

DR. PRZYGODZKI: That's right. Right.

DR. WEISS: Same device, no changes in between, everything's the same.

DR. PRZYGODZKI: Nothing?

DR. WEISS: So specificity-wise, they are fairly comparable, as we've seen, so around 80-ish, I would say, in both of those --

DR. PRZYGODZKI: Okay.

DR. WEISS: -- trials. And sensitivity-wise, I recall 68.2 in the pivotal trial, 72.2 also, as the FDA has shown in a nice summary slide.

DR. PRZYGODZKI: Okay.

DR. WEISS: Fairly comparable, same device, same testing, same procedure, nothing changed in between that process with the PMA submission.

DR. PRZYGODZKI: Excellent. Thank you.

Dr. McShane?

DR. McSHANE: I'm going to ask a question of Dr. Bujold because you were talking about your --

DR. PRZYGODZKI: I would actually like if we can do this -- the questions between the Panel a little bit later, and we monopolize as much time as we can --

DR. McSHANE: Okay.

DR. PRZYGODZKI: -- with the FDA and Sponsor.

DR. McSHANE: Okay. Well, I can direct it to the Sponsor also. They may have data on it. The question in my mind is we're sort of viewing this new test in front of us as a way to get people into screening. And so I'm curious if you have data on patients, you know, coming into a clinician's office and saying, okay, I'll agree to have you check off on your lab form, you know, all these blood tests, probably cholesterol and whatever else they always measure, and it's very easy for them to check another box for your test. How much data do you have, if any, on the experience of once you have that patient sitting in front of you and you're checking off the boxes, when you hand them the card and the stick for the fecal-based test, you know, how many of them will say, no, no, no, I'm not going to do that, but I'm happy to have you check any of the blood-based tests? Do you have data on that?

DR. TAAPKEN: Well, we do not have actual hard data in use with the device because, obviously, it's not on the market yet. So, what Dr. Heichman was presenting earlier in the public hearing, she was referring to a study, a survey that has been done with the Huntsman Cancer Center, so that's the only real data where we have some indication of preference for

different screening modalities in patients that have been informed about merits and risks or, you know, risk/benefits of both tests and performance levels actually, rather than risk/benefits of both tests. And based on that study, a blood-based option ranked fairly high in most scores there, so there seems to be clear trend towards preference of blood test over stool test for utilization and then adherence.

But it's hypothetical. As I said, the device is not yet on the market, so the real-life situation in a physician's office is not existing yet.

DR. McSHANE: Right. And I guess that was my concern, that it's one thing to just ask people hypothetically, but if you're talking about the population of people who are already sitting in the clinician's office and you're checking off the list, how many at that point, you know, would have voiced that preference. It wasn't clear to me from the figures that were presented earlier whether that was just, you know, hypothetically going to people and saying, if you were offered these two options, which would you prefer. So -- but you don't --

DR. TAAPKEN: No, that data --

DR. McSHANE: You don't really have details of that?

DR. TAAPKEN: We do not have that data, no.

DR. PRZYGODZKI: Next will be Dr. Hicks and Dr. Caggana and then Dr. Weck, please.

DR. HICKS: I have a question for Dr. Johnson. The question I

have, Dr. Johnson, if I come to your office and I need -- during a physical examination, getting my check-up and I'm over 50 years old, and you tell me I need to get the colonoscopy, and I say can't do it, for whatever reason I'm not going to do it, you say, well, I'd like you to get another test. So, you have two tests available, these two tests. Both tests have a sensitivity of about the same, but one has more false positives than the other test. Which test would you suggest I get? And if was high school math teacher and asked that question, and I said, you know, well, which one has fewer false positives, which one would you want me to take, which would you give me, suggest to me?

DR. JOHNSON: Well, sure, and recognize, too, that we have a menu of other options. So when we talk about stool tests versus blood tests, there's flexible sigmoidoscopy, CT colonography. There are a variety of other modalities that would be included in the discussion. So, there are other options. My job is to try and look at what test that you're willing to do, and if I have to take a test, that I know you're willing to do and complete it. And the default is, perhaps, that you have a higher referral rate for a colonoscopy. That's my preference to begin with. So, as a patient advocate and trying to get you to a colonoscopy, my goal is to get you screened. If I get you screened and the default is you have a higher false positive but no change in the sensitivity, then I'm going to default to that test.

DR. HICKS: Let's shift gears. Let's shift gears about this --

DR. JOHNSON: Sure.

DR. HICKS: What percentage of your patients have you ever had in your office tell you, I'm not going to give you a stool specimen, just say I won't do it, because I'll just tell you in advance, my experience, and I know Dr. Bujold's, hardly ever anybody won't do that.

DR. JOHNSON: Yeah. Again, as a gastroenterologist, we're referred patients for screening. So, it's rare for us to initiate the concept of screening discussions outside of people that maybe we pick up haven't been screened appropriately. So, we don't have as much of a direct, hands-on as a primary care base would. They'd be better to address that with the primary care folks.

The issue about fecal testing or some other test is when they say, okay, I took it, did they bring it back or send it back, and did they complete it? That's the gap that still is waiting to be defined, and really, fulfillment of the test.

DR. HICKS: Well, let's just say electronic records show that it came back, but which test are you going to suggest for me if I ask you that question? Which one has the least false positives? Are you going to suggest I want you to take the FIT test, or are you going to suggest I get a serum test?

DR. JOHNSON: Yeah, again, you're asking really specific questions that most of my patients don't ask me --

DR. HICKS: I think that's the idea --

DR. JOHNSON: Well, most of my patients don't ask me what has more false positives. They ask me what --

DR. HICKS: So, if you're going to suggest the test, and if they're not asking you, which one, just out of your own thoughtfulness, would you suggest to me? Would you suggest to me a test that has 20% fewer false positives, or you'd give me one that has 20% more false positives?

DR. JOHNSON: Well, I want to not compromise detection of cancer, so I start with that as a non-negotiable.

DR. HICKS: So which one would that be?

DR. JOHNSON: And then -- well, they're equal if we're talking about FIT and the Epi proColon. So we're talking about -- is that -- are those the two tests that you're asking my opinion?

DR. HICKS: Um-hum.

DR. JOHNSON: Okay. Again, clearly, my opinion, just based on what would I be defaulting to, would I take a false positive rate that would get more people into a screening modality or recognizing the default would lead to a higher detection of other things? I'd always take that.

DR. HICKS: But I'm not asking you that. I'm asking you which test would you suggest to me. I'll take either test. You're suggesting a test. Are you going to give me the one that's got 20% more false positives or the other one? Which test are you going to suggest to me?

DR. JOHNSON: I think that's an informed discussion where the

patient asks me what does false positive mean. And I say, well, the false positive is a number. But let's understand that and put that in clinical perspective. What does that mean? You may get a colonoscopy that didn't find a cancer, but you had a 40% or 50% incidence of colon polyps, prevalence of colon polyps that we might discover otherwise. So I think there's no white and black in a discussion like this. I think it's an informed discussion about --

DR. PRZYGODZKI: Right. So at this point, it seems basically we've gone to -- impasse --

DR. TAAPKEN: Sorry.

DR. PRZYGODZKI: Yes?

DR. TAAPKEN: I would like -- to the last question, I would like to add one more, I think, quite important comment.

DR. PRZYGODZKI: Sure.

DR. TAAPKEN: When we were asked to do a comparison trial between Epi proColon and the FIT test, we were starting to also look into the literature and look at comparable data between the performance of FIT tests. What we found in the literature is quite a vast array of different data that had been generated in very different clinical settings, which, for us, was very difficult to assess which one is actually the one that we should be using to compare ourselves with.

So, what we did is we picked what we believed is the market-leading product here, which had the best-described clinical performance. But

I don't think there is a -- we should not -- or we should be careful making the assumption that each FIT test is equivalent to each other FIT test. There are self-administered tests. There are tests that are run in the laboratory. There are different modalities on how fecal immunochemical testing is done. And I think in the whole discussion, what gets forgotten sometimes is the fact that we have compared ourselves just to one that we considered to be one of the best performing ones. Just as a comment.

DR. PRZYGODZKI: Thank you.

To continue with Panel and FDA questions, I think actually Dr. Caggana was up next.

DR. CAGGANA: I just have some questions on the actual test, if I could ask them. How often is the test actually, in practice, invalid? And you just would go ahead and ask for another blood sample? I thought in one of the studies, it was fairly high.

DR. TAAPKEN: Can ask Dr. Weiss this question?

DR. WEISS: So, I guess the best data from real-life comes from our pivotal trial, and we might have that slide showing the data. If not, I recall that we tested -- started testing 1,623 specimens and had 1,544 valid results. So we lost 79 during the course of the analysis. It was a real-life setting, I would say, free independent labs here in the U.S. who ran those specimens.

I also recall that from the specimen quality, it was a small

minority, say, a dozen, 13, I believe, where the sample was not good enough and was -- in terms of providing a valid β-actin result, that internal control, and the remainder of those invalid tests were due to invalid process controls. So, we interpret this as some sort of a handling error or an issue with the device. So, we had during that trial a couple of runs where the PCR device, actually, due to power outage, broke down. So these things happen.

But as a matter of fact -- slide up, please -- we see that I'm not too bad in numbers, I assume. So 79 are those total number of substrates with no result. You see that in the bowed number on the right-hand side. And 13 of those which I was referring to as being invalid test results, and that's due to the specimen quality, basically, where we like to make sure with this control that there is DNA extracted, bisulfate converted such -- something could be assayed.

DR. CAGGANA: Right, right -- information on different parts of the test.

DR. WEISS: Yeah.

DR. CAGGANA: Sort of counterintuitive, I guess, because we're talking about false positives, but in one of the summaries, there was some information on some SNPs that were found in the area that gets amplified. Did you do any kind of modeling where you created an oligo that contained those to see whether or not the assay worked, because I think you cited in some part that the SNP frequency was very rare, but if one in three people in

the U.S. might uptake this test, that's not that rare, where you might have trouble with the assay itself?

DR. WEISS: So, it is my understanding that the SNP, which is in this region, we have designed oligos such that the SNP is not recognized. So the amplification of the target is not affected by the SNPs.

DR. CAGGANA: And not by the methylation or the blocker or the primer --

DR. WEISS: Yeah, so the SNPs we are aware of have been taken into account into the oligo design -- primers, probes, and the blocker bit.

DR. CAGGANA: Okay. Just a couple more questions. One more? Okay. So getting back to the earlier question on the fact that in the healthy population, there wasn't real good reproducibility, did you look at copy numbers? I know you just -- you know, when you get past a certain point, you can't really look at copy number, but did you [look at] percent CVs on the Cts and replicate samples or something like that to show that -- I'm trying to get a sense of when you have these replicates and you have a fail, do -- are the Cts very close, because the Ct is a lot different than a copy number at a low end of sensitivity.

DR. WEISS: So, I think the FDA presented it fairly nicely. In the reproducibility study for those, say, healthy pools --

DR. CAGGANA: Right.

DR. WEISS: -- there were hardly any PCR curves to study. So

those false positives are rare events. They're single curves. They're late. And so there, it's hard to do any standard deviations or coefficient of variation calculations. For those where we have solid data -- and I might provide you with this detail that this reproducibility study was not just done on cancer pools of any kind, but we also challenged the process by diluting cancer into --

DR. CAGGANA: Right.

DR. WEISS: -- human plasma really to get to the end where the assay might be struggling. We provided these kinds of data of coefficient of variation and standard deviation. I think they're fairly solid and --

DR. CAGGANA: Okay.

DR. WEISS: -- maybe the FDA wants to comment --

DR. CAGGANA: The FDA saw that, okay.

DR. WEISS: Saw that, I guess, in the appendix of the summary, of the FDA's Executive Summary.

DR. CAGGANA: Okay. Thank you.

DR. PRZYGODZKI: Okay. We have roughly about 15 minutes that I would like for the Panel to speak among themselves with what we have heard from the morning from the Sponsor, from FDA, and questions in general, so we can shoot at each other with these points that we wanted to illustrate and identify among ourselves, as we all have some expertise in specific areas and we can share this knowledge.

I would ask that you identify yourself so the transcriptionist can take the name of course, but 15 minutes, and folks, let's have it.

Dr. Nostrant?

DR. NOSTRANT: I guess I'm going to bring up one situation that I think we haven't thought about. The highest test that we're talking about that has the highest false positive rate is colonoscopy, highest false positive rate. Give you an example. If you do an average-risk colonoscopy, the chance you'll have a cancer is 1 in 125, which interestingly enough is -- the number here is 1 in 133 to get the 50 evaluable cases of colon cancer. If you have bleeding, the chance is 1 in 40. That means 39 of 40 are going to be false positives, okay, for cancer. And then on the third side, if you have anemia, where we would think that colon cancer is extremely, it's 1 in 8 -- I mean 7 out of 8 patients are going to be false positives. So, in actual fact, this test -- remember these are point indices. I'm not going to talk about longitudinal here. So, the argument would be is that this is actually reducing the number of false positives, not increasing the number of false positives because it's going down to 19,000.

DR. SKATES: I guess -- sorry, this is Steven Skates. In terms of false positive definition, the test has to say there's a cancer there and it turns out on surgery or pathology it was wrong. So, I don't think colonoscopy has a false positive rate of 99% or -- that's not what the definition of a false positive is, so --

DR. NOSTRANT: Oh, no, I'm talking about --

DR. SKATES: Whereas Septin9, we'll say it's a positive test, and you don't have cancer, as defined by the gold standard of colonoscopy or, at least, that's the gold standard that I'm going on at the moment, and even that's not perfect, we know that, but it is far more accurate. And of the three tests here, we'd consider it's close to the gold standard. So I just get -- my issue is the definition of false positive here.

DR. GALLAGHER: Colleen Gallagher. I think one of the questions that -- I come at this from a different background a little bit. I have a background as a social worker as well. So I'm thinking -- I'm hearing risk all in terms of medical things only. And I think the psychological and psychosocial things are also medical in a way. And so I think that discussion of false positive results with a patient can be very difficult. And so encountering the patients that I have that are kind of in crisis when I see them most of the time, because they've gotten some news and they don't know what to do with it, I'm thinking of a patient who might perhaps go do this test because this is easier than doing a colonoscopy, right? That's my first screening test. I might choose it. And then I'm going to go get the colonoscopy. That comes back, no, I don't have this. But I'm smart enough to be an internet user, and I might see that, you know, Septin9 is something that is also evident in other cancers and other diseases.

So, how is the doctor going to talk to me when I ask those

questions, or even if I don't? Is the doctor going to talk to me about, well, then maybe should I be screened for lung cancer, should I be screened for some of these other diseases. So I guess I'm just seeing the risk factor of false positive from we're only talking about one side, but then also, clinically, how does a physician handle that kind of discussion?

DR. WECK: Karen Weck, University of North Carolina. So I just wanted to get to the issue of the intended use of this test, which, as stated, is to use as a screening test for individuals of normal risk or average risk of colon cancer. And so, you know, what I want out of a screening test is a test that's going to detect everyone. And so I'm much more concerned about the sensitivity than the specificity. That's the way newborn screening is. I mean, a screening test should be something that's very sensitive so that you pick up as many people as possible and define those that need to go on to more diagnostic or gold standard testing such as colonoscopy.

So, you know, I think a sensitivity of 70% in, in my mind, not really adequate as a screening test, you know? The problem is that there are not really accurate screening tests for colon cancer. What we have is the FIT test, which has a similar sensitivity. This performs really no better than the FIT test in sensitivity, but the FIT test is more specific, as we've seen. So, we're going to have about an equal number of false negatives between the two tests, but way more false positives with this test. So, I don't think that really to me is a safety issue, because although there are risks of

colonoscopy, those individuals should be getting colonoscopy anyway. So, the false positives essentially would be triggering people to get colonoscopy.

I'm more concerned about the false negatives. So, of the 100 people that are screened with this test, 30 of them would be false negative and would, I think, perhaps be, you know, be given a false sense of security that they do not have colon cancer. So that, to me, says it's not really an effective screening test.

In comparison with the FIT test, I think, you know, we've been discussing a lot that patients may rather have a needle stick than give a stool sample. There hasn't really been any data to that regard. And so given the two tests, I think FIT is the more accurate test, because it has a better specificity.

I am intrigued, however, with the data that the FDA presented about using the two tests in conjunction, so I think the wording was the "Believe the Positive." So if you use the two tests together, you may be able to increase the sensitivity dramatically without taking a huge hit on the specificity or on the number of false positives. But the intended use as it is now, as a screening test on its own, I don't see a compelling argument that it's really an effective screening test.

I would be intrigued, though, by the idea of, you know, in other studies perhaps, looking at, you know, so if another prospective study was done looking at yearly testing with this test, perhaps including an arm that

used both this plus the FIT test together to see if the sensitivity for screening could be improved in that regard. And it looked from the initial calculations that you didn't really take a huge hit on specificity and that there was even possibly improved both positive and negative predictive value in using the two tests together. But that's not what we're discussing today.

DR. McSHANE: I'd just like to follow up on what -- oh, Lisa McShane -- I'd just like to follow up on what Karen just said. I agree with what you just said, and to me, the big risk here is not the false positives. The biggest risk in my eyes is, you know, this, if it's approved, would be the second test on the market that says, hey, you don't really need to get the colonoscopy; just go ahead and get a blood draw, do the fecal test. And I guess I would be really curious and nervous that what might happen is that, suddenly, the rates of colonoscopy acceptance would start going down, because people say, hey, I don't want to have to do that colonoscopy thing. I can just go get one of these other easy tests. Now, in some sense, that would not be fair to this company because there's already a test out there that has comparable properties, and may be a little better, at least in terms of the false positives. But, you know, that's the one I'm really struggling with.

DR. GATES: David Gates. I don't know. I don't really share that because to my mind -- well, I think it's kind of speculative. It's hard to say what they're going to do under certain conditions. I think we have to kind of focus on what the indications are.

In terms of the sensitivity, to my mind, they're about the same, and the fact that you may get a compliance advantage kind of weighs the other way in the sense that, given the fact that they're about the same sensitivities, or for whatever reason, a blood-based tests allows people to get more testing, in terms of compliance, I think you come out ahead under those conditions.

DR. MAHOWALD: I was intrigued earlier with Dr. McShane's question about the pool of people who are neither screened nor tested, because I wonder how we determine that ratio of people who are actually refusing or are actually just not involved in the system or not interested in the system who are not actually refusing. And I couple that with Dr. Bujold remark about this 70% increase. That's of patients who you see whom you talk to. And it makes me wonder whether this whole effort to introduce a screening mechanism, which is to people who come to clinicians, is in a sense evading the crucial educative function of the doctor himself or herself who does hold that the gold standard is colonoscopy.

I mean, certainly, the physicians that I've worked with over many years, at least many of them, will acknowledge that what they most heartily recommend to a patient is very typically accepted on the basis of that recommendation. And so throughout a lot of this discussion, I was kind of wondering in my mind how many people really come to doctors, you know, truly informed about differences in tests, differences in terms of risks of not

knowing or being tested in a certain way, who absolutely refuse, don't just say like I would, I don't want a colonoscopy, but say I absolutely refuse what you heartily recommend as the gold standard.

DR. NOSTRANT: I'll give you my own perspective. Oh, Tim Nostrant, GI, so you'll have a real perspective of potential bias here. What I tell my fellow and my patients is all God's children need a colonoscopy. It's just a matter of time. And what I tell them is the risks and the benefits of all these tests. And despite all of that -- my wife's a social anthropologist and came in and did a study as a social anthropologist and found out several populations, Muslims, will not do colonoscopy, because it requires removal of gowns. There's a lot of social issues and cultural issues.

So, the question comes down to -- is that there are people who refuse. I have people who have inflammatory bowel disease who refuse a colonoscopy for colon cancer when they're symptomatic. So the argument is people will refuse. So, I guess the question here is, that population there, I wish they would have studied the population that actually refused, but I think they've done the best job in doing that. And I don't think you're going to get a better population to study there because it's going to be difficult to do.

I agree the physician will make a big difference, but it's in the group who's going to follows a physician's directions when they see them, not necessarily the people who have cultural or other --

DR. MAHOWALD: That's true --

DR. NOSTRANT: Right? And cost is another issue that we haven't talked -- so --

DR. HICKS: Terry Hicks, surgeon. And I apologize for -- Dr. Weck, I had a question for you, because I think you led to a good point about we already have this test, we have that test. I'm still confused about the actual sensitivity of the FIT test. If you look, you know, from their reports, they say it's as high as 87%, you know, for detection of colon cancer. It's all over the map in some of these, so when we try to compare and be fair to the Sponsors here today, you know, I'm not really sure what the number is. But it's reported as 87, but with a 97% specificity. So that would be interesting.

And so I'm going to have to get with our statisticians at the break and all, but there's been a recent article that was written in the *International Journal of Colorectal Disease* about the sensitivity and specificity of the immunochemical blood testing, and we can look at the stats and see if the stats are any good, because invariably we end up looking at this, and then we find out that wasn't done well. So have to get Dr. McShane and Dr. Skates' approval.

DR. GALLAGHER: So, while I still have my concern about the false positives and those conversations, I also do a lot of work looking at health disparities. And I think that Dr. Weck's questions or statements about looking at this as a screening mechanism for the regular population at normal

risk, or whatever, could you help me understand what you think a high enough rate would be? Because I'm thinking about those patients in neighborhoods or whatever who don't normally go to the doctor that have -- we have outreach programs that go out to them that might be able to use this as a screening mechanism to even get them into the system if need be. So, I just want to have an understanding of that, please.

DR. WECK: Well, in terms of a screening test, I mean, it's impossible to have a test with 100% sensitivity and specificity. So, you know, that is a given. But a sensitivity of 70%, such that 30 out of every 100 people screened would be falsely negative, just, you know, seems too low as a screening test. So, you know, the Sponsors indicate that those individuals would still be recommended to have colonoscopy. So, colonoscopy would still be recommended in individuals who test positive by this test and in individuals who test negative by this test. So, it's unclear to me what really is the clinical utility of this test then.

In terms of what would be an acceptable sensitivity for a screening test, I would say, you know, at least 80%, between 80 and 90% would be ideal. You're going to miss some people obviously, but it's just not a compelling argument to me to use a test as a screening test if you're just trying to identify people who should be getting the test that you're already recommending.

You know, I mean, if you could do this -- the only compelling

argument to me is that since colonoscopy is recommended only every 10 years and you may miss people in that interim, you know, is there a test that you could do more frequently that would pick up, you know, a large proportion of people. So, I'm not saying we should do nothing, but we have the FIT test, and that seems a superior test, based on the specificity.

DR. PRZYGODZKI: We need to slowly wrap up, maybe two or three more questions.

DR. SKATES: So this -- various people on the -- this is Steven Skates -- various people on the Panel have put out what they're struggling with thoughts, and I'd like to do that myself. The positives I see here are another way of doing this test, a blood test, which may be more acceptable than a stool test or a colonoscopy. So, there is the argument of having more people participate. It would be very helpful had the Sponsor had data on such a question, that there was preference -- or not just preference, but actual action of doing that.

The other positive is that it's a test that could be done more frequently than colonoscopies. And so that may actually increase the sensitivity over time like Dr. Ransohoff and others have pointed out. So, that's the plus side that I see. Unfortunately, the plus side doesn't have the data there to back it up. It has an argument and a rationale, but no data.

On the negative side is, compared to the FIT test, is a much greater, seven times many more false positives. So, 1 in 5 patients without

any colorectal cancer will be told they have a positive test. I see that as a big downside. What I'm struggling with is to assert that it's not safe, therefor, or it's not effective, because neither safety nor effectiveness are supposed to be, at least in my understanding, against another test. It's supposed to be a standalone assessment.

So, if anything, the safety is on the issue that Dr. Gallagher brought up of the anxiety and the concern as to what do I do next if I've got a positive test because I might have other cancers or I might have other diseases, or I don't want to go for a colonoscopy in the first place. So balancing that negative with those potential positives is where I'm at. And it's a difficult decision particularly on the repeat test without any repeat data.

DR. PRZYGODZKI: Please.

MS. FURLONG: So just from a practical point of view of a person who is not --

DR. PRZYGODZKI: Please identify yourself.

MS. FURLONG: Oh, I'm sorry. Pat Furlong, Consumer advocate.

Just from a practical standpoint of going to the doctor or being unwilling to do a colonoscopy or people who are taking advantage, if you think it's an advantage, of going to the clinics that are in, for instance, Walmart or Walgreens, which is minimal medical care, I feel like as a consumer, I'd like an arsenal of tests. I'd like to know that there are a

number of tests that are going to help me or that are going to provide options so that I can maybe become interested in tests that I need or I should have at a given age. I would also sort of suggest that if I have a colonoscopy, if I am that involved, and then I'm told 10 years from now, you have to get this, I would kind of wash my hands and say, good, 10 years from now I'll be fine. And it is perhaps unlikely that that is the case or that's going to be true.

So, from my standpoint as a consumer, I like to know that there are several tests available that will give me a reasonable predictive possibility of my going further and get me interested in my healthcare. So, I don't disagree the false negatives -- the false positives are worrisome, but I also think for some people, it's necessary to get them engaged. So, you know, I just feel having more than one test, more than a single FIT test might be useful as we try to really better understand who is at risk and how to diagnose them.

DR. SKATES: Just to respond to that -- this is Steve Skates -- would you not be more reassured if there were data on that, which might take six months or a year to get?

MS. FURLONG: Of course. I would be much more reassured with more data. Of course.

DR. SKATES: Because there's none at the moment.

MS. FURLONG: Right. Exactly.

DR. NOSTRANT: I guess I would make one comment --

DR. PRZYGODZKI: Please identify yourself, and you'll be the final comment --

DR. NOSTRANT: Oh, Tim Nostrant, I'm sorry, University of Michigan. John -- or Dave Johnson actually showed John Adomi's (ph.) study, which showed that number of choices was directly related to participation, okay? So I agree with you wholeheartedly that, even though I would recommend a colonoscopy, having a choice to getting those populations that might refuse in is really quite interesting. I really think we should be doing more. And I can't get patients to do the FIT exam because it requires multiple stool and collection every year. It's very difficult to be effective. Even going a second year is -- you lose the utility of the test.

So, the argument here is that really choice is appropriate to get them in, because then when you have them in and if they're positive and get a colonoscopy, they rarely refuse that subsequently because they then know that the test is relatively easy to do. So I agree completely.

DR. PRZYGODZKI: Okay. One final question, please?

MS. DeLUCA: I have two short factoids. The new American Cancer Society *Facts and Figures* came out this past week. One of them stated that 35% of people over the age of 50 participated in no screening for colon cancer. 35%. That's horrendous. And the other one follows it up. 60% of the cases that were diagnosed are in late stage, 3 and 4. That's a horrible boat to be in. So this might --

DR. PRZYGODZKI: Okay. Thank you.

So, right now, we're going to take a 20-minute break, and we will be back at 20 till 3. Thank you.

(Off the record.)

(On the record.)

DR. PRZYGODZKI: So, this is the time that we're going to sit down and review and discuss the FDA questions. Panel Members, the questions are in your folder. They are in the agenda. Somewhere in there you will find specific questions as they have been noted. There are four questions in here.

And the process will be that we'll have presentation of what the questions are, and we're going to go in individual sections through this. And I will go through with some of you folks and see if there is -- if there is a consensus, we can ask are there issues that others may identify that we need to add or that you are negating or supportive of, and then we'll go on this. I will reiterate the commentary that you folks have given to Dr. Gutierrez. And then we'll go to the next question.

So it'll be rather rote. It's important for us to have the clarification and FDA to understand what our assessment of the whole process is at this point.

So, can we go with the first question, please?

DR. LEE: Okay. Thank you. Before I read the questions, I

would like to note that please consider these discussion questions in the context of the proposed intended use. And if you have any suggestions with respect to the intended use, then we are happy to hear that, and we welcome those suggestions and discussion.

Question 1: In the pivotal trial, Epi proColon has a sensitivity of 68% (with a 95% confidence interval from 53% to 80%) and a specificity of 79% (with a 95% confidence interval from 77% to 81%). In the FIT comparison study to assess non-inferiority of Epi proColon, the goal for sensitivity was met, but the goal for specificity was not achieved. The decreased specificity of Epi proColon was not associated with a clear benefit in sensitivity when compared to a commercially available FIT test. The lower specificity could lead to an increase in the number of avoidable colonoscopies. While colonoscopies are considered the standard of care and recommended in CRC screening guidelines, there are adverse events associated with such invasive procedures. In the non-clinical studies, non-CRC specimens are not consistently detected by Epi proColon. In addition, there are some other cancer types for which methylated Septin9 is detected by Epi proColon.

a. Do these outcomes adequately demonstrate effectiveness of Epi proColon within the context of the proposed intended use and current recommendations for colorectal cancer screening?

b. If yes, do the data support screening with Epi proColon as (i) a second-line option only in patients declining FIT, (ii) an alternative for FIT, or (iii) some other option?

c. Based on the results of the pivotal and supplemental clinical studies, do the data allow for adequate assessment of the benefits versus risks of Epi proColon?

DR. PRZYGODZKI: Thank you. So let's take a look at (a). Dr. Nostrant, your thoughts?

DR. NOSTRANT: I think it does adequately demonstrate effectiveness. Again, the definition of effectiveness is always an argument here. As posed by the question, there's a clear concern about the specificity of this. My argument is I'm not terribly worried about that, and I'm much more worried about sensitivity. And sensitivity appears to be equal to FIT and is an option that many patients will accept over FIT because it's a blood versus fecal exam. So, I think it does meet the intended use.

But if I were -- to the second part of the question, I'm probably going to have another answer to -- but the second part, I think, is it better than FIT or it should be a alternative to FIT --

DR. PRZYGODZKI: Let's stick with (a) first and get a --

DR. NOSTRANT: Okay. That's all -- that's a yes.

DR. PRZYGODZKI: How about Dr. Weck? I'm randomly picking people. Believe me, most people are going to get touched.

DR. WECK: Well, I would have to say no. In my opinion, the outcomes do not adequately demonstrate effectiveness of this test as a screening for colorectal cancer due to the sensitivity issues we discussed early, and then, in addition, due to the decreased specificity compared with the FIT test. So, I guess we can talk in a minute about whether the data might support an alternative to FIT. Okay.

DR. PRZYGODZKI: Okay. Dr. Mahowald? Dr. Mahowald, please?

DR. MAHOWALD: Mahowald.

DR. PRZYGODZKI: Mahowald, I'm sorry. I got problems with my own name, so hey.

DR. MAHOWALD: Yeah, I guess I believe these outcomes adequately demonstrate the effectiveness within the context of the intended use, which is pretty limited. I think a key word there is "adequately" demonstrates. I would not have substituted the adverb "compellingly," but I think the test is safe and it provides useful information that may obviate the resistance of some patients to go through with the FIT test, let alone colonoscopy later on. And so I would agree with Dr. Nostrant on that.

DR. PRZYGODZKI: Dr. Skates?

DR. SKATES: I believe these outcomes don't adequately demonstrate the effectiveness within the context proposed, so that is general-risk population screening. The compelling argument that the

Sponsor has made was that they'd close the gap that weren't using the test, and I didn't see that really being adequately demonstrated. And I saw that as part of the effectiveness of Epi proColon.

DR. PRZYGODZKI: Dr. Bujold?

DR. BUJOLD: Oh, I'm sorry. I would concur with Dr. Weck and Dr. Skates.

DR. PRZYGODZKI: Dr. McShane?

DR. McSHANE: I would also concur with the last -- with Dr. Weck and Dr. Bujold and Dr. Skates, because I view effectiveness as the entire picture of is it effective to use this test to get the right people to get screened, and I'm -- I think that that requires looking more -- looking at more than just who is offered this test and who goes and gets it and who is diagnosed with colon cancer. I think it could have other ramifications that we maybe are not fully appreciating.

DR. PRZYGODZKI: Are there folks -- it seems to me that, you know, there are more -- looking at this conversation and the previous conversation, that there are more folks that are not as supportive of this as being a screening type of test. Are there people that would like to say that I am incorrect in that assumption?

Please, Dr. Gates?

DR. GATES: Yeah. I would have to think and say that it is. I'd have to disagree with Dr. Weck for a couple different reasons. One is I'm

familiar with an HPV test for primary screening that just went out. We had, at that point, a sensitivity of 68 -- or of 60 -- I'm sorry -- 58 to 60. And the issues is, is there anything else on the market that's any better, any other test modality that's any better, and there isn't. And I think in the same situation, we're faced with the same situation here. Yeah, everybody would like to have 100% sensitivity and specificity, but it depends on what the context is, as FDA has mentioned, and within the context of a noninvasive test, the sensitivity is about what would be expected for a screening test. Other advantage of having two tests, even if they're the same, is that it, as it was raised before by, I think, Ms. DeLuca, that you want to give people an option. And to the extent that you're giving people an option between a blood-based test and a stool-based test, I think that's a good thing, given that they're equal.

On the issue of specificity, I also think that, from my point of view, from what I've heard, and obviously I'm not a gastroenterologist or a physician, but it makes sense to me that where this test differs from other tests in terms of specificity is that the alternative is the current standard of care, and what you're trying to do is get people to get colposcopies, and to the extent that, from what I can see, there's not very many adverse effects involved, and to the extent that it would reflex into colposcopy, which is where you're trying to get people to begin with, that specificity is not really an issue in this case.

DR. SKATES: Colonoscopies.

DR. GATES: I'm sorry. Yeah, I'm thinking of the HPV stuff. I'm sorry. I've still got that in my head. Colonoscopy, excuse me.

(Laughter.)

DR. GATES: So, from that point of view, I don't think that specificity would be an issue.

DR. PRZYGODZKI: Okay. Very good.

Please, Dr. Gallagher?

DR. GALLAGHER: Colleen Gallagher, I think that, for me, the difference comes in the idea of the intended use, specifically. So if altered slightly, I think I could say yes to it doing this. So, I think as a general screening tool for the large population and making that a major screening tool, that I have a little bit of trouble with, but if you -- if they were able to say something about for those persons who specifically refused colonoscopy or weren't able to -- like, specify a little better the intended use, I think, then, I would be able to easily say that it had some effective -- it was adequately effective to do that. But as a general screening tool, looking for 75 to 80% as a minimum is what I usually use, then it doesn't. So I think change the definition a little bit.

DR. PRZYGODZKI: Others? Please?

DR. LIPKIN: So, yeah, this is a test, there's a lot of gray here. It's clearly not sort of black and white, and I think that's why we're all kind of

struggling a little bit, and there are good arguments on both sides. I'm now going to make problems for the audiovisual person because I want, actually, discussion question (b) up as well. Can we forward it? Thank you. Okay. Good. So I'm actually going to slightly go off -- thank you -- perfect. I'm going to go off script here a little bit, and I'm going to say that I'm going to answer (b) first --

DR. PRZYGODZKI: Not too far, please.

(Laughter.)

DR. LIPKIN: I'm going to go to (b) then (a), all right.

DR. PRZYGODZKI: Okay.

DR. LIPKIN: So, clearly, the data, in my mind at least, you know, support that this is -- actually would be useful as a second-line option in patients either as an alternative to FIT, patients who decline FIT -- the test itself is technically very impressive. It would be the first methylation test. There's a lot of, you know, I think, very, very impressive things to say about it, and the study that's been done is large.

But I'm troubled by the issues that have risen here, discussion of this using it pretty much, you know, as an indication for everyone over the age of 50, which includes, in fact, patients who are actually, you know, somewhat even a little ambiguous as to their high- versus low-risk status.

For example, under the proposed indications, patients who had colon cancer -- excuse me -- who had one first degree relative over 50 would

be eligible. We now know from the standpoint of genetics that a lot of patients who have, for instance, Lynch Syndrome and in the panels we now have 14 genes and such, and 20 genes, whatever, 25 genes, you know, for looking at inherited test -- for testing, that, in fact, the number of mutation carriers is actually higher, but the penetrance estimates are lower. Similarly, also included in this population are patients -- excuse me -- would be screened who have two second-degree relatives, okay?

So it bothers me that the patient population, once again, that's defined is so broad, and if it could be somehow honed down more specifically, and in my personal view, particularly serve as an alternative to FIT, I would be very enthusiastic. But with the proposed indication, intended use, I have diminished enthusiasm.

DR. PRZYGODZKI: So with respect to (a), are you supportive or no?

DR. LIPKIN: No to (a), but yes to (b), although the question says (a) has to be yes to (b), so that's why I wanted to discuss (b) --

DR. PRZYGODZKI: I understand.

DR. LIPKIN: -- before (a).

DR. PRZYGODZKI: Well, there are gray areas, no doubt. So it appears that there may be more of a mixed view, if I understand the Panel, of (a). That is, there are some individuals that view this as a good test because it is yet a different view and way of doing this testing that may be easier for

the patients, more accessible, and because of that, there may be an apparent heightened ability to have more screening done on these folks. On the other hand, some members have brought this up that the sensitivity is not high enough for a screening test, and because of that, there is the question of could this be as a first-line screening test, and that may be probably no. Could it be used, as some Panel Members have identified, could it be used as a secondary or a combined type of test, there is more favor, from what I see of the Panel, that that is more in tune of what that would be.

Does that fit sort of what the group is looking at? Yes?

DR. MAHOWALD: See, I agree with Dr. Lipkin, but my point is -- and I would have underlined number 2 under (b), but given that I underlined 2 under (b), I think I have to answer yes to number 1; (b) given underlined 2 is contextualizing my answer to (a).

DR. PRZYGODZKI: Okay. So, in that case, if we were to move to Question (b) --

DR. GATES: David Gates. I just had a question on the sensitivity. I mean, if we're arguing that the sensitivity isn't high enough, what's the alternative in terms of a noninvasive test that would have a higher sensitivity if we've shown here that any other noninvasive test is about the same?

DR. WECK: Well, I agree with your argument about HPV, that a sensitivity under 70% is acceptable because there was no alternative. In this

case, the sensitivity is, I would say, equal to FIT, but because of the superiority of FIT in specificity, it seems to me that that's the better test. So coming to (b), I would say that the data in my mind may support screening as a second-line option only in patients declining FIT. Otherwise, I wouldn't offer it as an alternative to FIT, a choice, but really only in patients who are not willing to give a stool sample.

And I just want to follow up on Ron's question about using it kind of in conjunction with the FIT test and looking at the "Believe the Positive." I think that that is an intriguing possibility, but we would need data to --

DR. PRZYGODZKI: True.

DR. WECK: -- indicate whether that was more effective or more sensitive.

DR. PRZYGODZKI: That's quite true.

Yes, Dr. Gates?

DR. GATES: And just not to belabor the point, but to follow up on the specificity, what would be the advantage of having a better specificity given the fact that they would go to colonoscopy anyway?

DR. WECK: The argument that they would go to colonoscopy anyway is not compelling to me, in this case, because it's being recommended in both patients who test positive and in patients who test negative. So, the false positive results would bring with it, you know, maybe

an increase in worry and other things about the individual regardless of whether they go to colonoscopy or not.

DR. PRZYGODZKI: That's true. It seems that there's a heightened sort of psychosocial kind of aspect to this that will be produced regardless. Then, again, when you look at the perspective of doing one test that is pretty good and a second test that may be pretty good, and regardless, everybody goes to, you know, to colonoscopy, why not just do colonoscopy?

DR. WECK: Right.

DR. PRZYGODZKI: And if that's the case, then, obviously we're not doing that. So having one test that's good and another one that's comparable, yet the -- as has been noted, the findings vary from patient population, or even within unique population that the study has been done, you get variety of Epi proColon positive, FIT negative, and vice versa, and yet these were in the specific categories. It makes one wonder if introduction of another test may be that beneficial, or would it introduce more noise into the system of actually screening individuals unless they were working together to do something like that. Then, again, this is just an opinion.

Yes, please?

DR. CAGGANA: Michele Caggana. I think have to loop it back around to the intended use because I think that's where a lot of people are tripping up. So, as the intended use is written here, it's written for the whole

population. When we start parsing out populations, if we had the data to study it, we could see where this test actually may be of a better benefit, so I think we have to keep remembering what we're gauging it against.

DR. LIPKIN: And a quick comment? Lipkin, here. Sorry. Quick comment. We didn't discuss this earlier, but one thing that -- and, you know, subset analysis is always a little tricky, and I just want to point out the difference between the U.S. and the German aspect. So, Germany has many cultural similarities, also some differences obviously, from the way things are done in the U.S. You know, half of the cases that were picked up were in Germany. So there's an 83% sensitivity versus 58% in the U.S. Now, we know that, you know, it's not statistically significant in subsets and all these other issues are absolutely correct. But it's a little concerning just that, in summary, we're talking about this issue of is 70% enough. And a lot of that is driven by things outside the United States. And here we're talking about a test in the United States. So that is -- it's not a black and white thing, but it troubles me a little bit. But does it trouble anyone else or no?

DR. PRZYGODZKI: Okay. Yes, please?

DR. SKATES: Just to answer this issue of adequately -- do the outcomes adequately demonstrate the effectiveness, it seems to me that the gap that they are trying to overcome could be -- we don't have data on it. We have speculation. We have rationale. And so in (b), do the data support this? I'd say there's a gap there that I think the Sponsors could actually

address in fairly short order in terms of a small study that would go a long way to essentially, presumably supporting the rationale that they have put forward here. And so I don't see that as a major impediment to this eventually getting to the patient. I see it as something that will solidify their rationale at the moment.

DR. PRZYGODZKI: Dr. Gutierrez?

DR. GUTIERREZ: Could you elaborate a little bit more on what sort of study you're talking about?

DR. SKATES: Steven Skates again. So in patients that come in to primary care physicians who are older than 50 and fit the general risk population who are advised to go to a colon test, refuse it, and then advised to go to a stool test or are offered a stool test and refuse that, then what fraction of those patients actually take a blood test and follow through and actually do that blood test for Epi proColon. If there was a very small number, you know, less than 5% of those who took the test, then I'd say that wouldn't support it, but if there was anything appreciable, 20% or greater, I would say that that would make -- support their argument.

DR. LIPKIN: Lipkin. I do think that the concerns are actually very easily addressable with additional studies, and the kind of difficult part here is we're saying should this be pre-approval or is it something that could be part of a post-approval study. And that's kind of the head-scratcher.

DR. NOSTRANT: Could I ask just one question? If this was FIT

coming up, how many people would have approved FIT?

(Laughter.)

DR. PRZYGODZKI: That's probably not a part of the question at this point, but I think Dr. Gutierrez looks like he wants to say something.

DR. GUTIERREZ: Yeah. It's not part of the question, but I guess it is useful to know that FIT didn't go through this. FIT came as a substantial equivalent and actually never answered these type of questions.

DR. WECK: So my understanding that FIT --

DR. GUTIERREZ: That's right. That's what I mean. It's substantially equivalent to something else. It doesn't have this intended use. So, it never went through an intended use type of study like this one that would have left you with a knowledge of what its performance is for this intended use.

DR. WECK: Right.

DR. SKATES: So, then, what was it equivalent to? You said it went through an equivalent use -- study.

DR. WECK: I believe FIT was compared to the guaiac fecal occult blood test?

DR. GUTIERREZ: The fecal occult has been a longstanding test that has become a practice of medicine to use as a screening test for this.

DR. WECK: Right. My understanding is that the FIT test was cleared because it had superior specificity to the guaiac test. And so what

we're looking at here is a test that may seem to me to be more similar to the old guaiac fecal occult blood test in that it has similar sensitivity to the FIT test, but decreased specificity. So, you know, I just -- I guess I'm just wondering if we're going backwards.

DR. PRZYGODZKI: So, before we go any further, let's focus on (b), and is this a second-line option only in patients declining FIT, an alternative to FIT, or are there other options? Can we focus on that?

Yes, Dr. Gates, please?

DR. GATES: Well, yeah, and just it kind of segues into what just got said. It doesn't seem like it should be a second-line option. If the first-line option was done on a 510(k) where the bar is a lot lower and, essentially you just have to show that it's substantially equivalent to something else out there -- I think this is unique, and that's why we're here in a panel, is that this has to stand alone for safety and efficacy by itself. And so to say it's a -- it seems to me kind of backwards to say that a PMA Panel-based evaluation carries less weight than a 510(k) substantially equivalent test. Doesn't make sense to me.

DR. PRZYGODZKI: No, that's -- of course --

DR. GUTIERREZ: Can I take a whack at that?

So the FIT and the fecal occult blood test do not have this intended use. They can't claim this. They can't. So, the fact that it is being used as practice of medicine for this intended use is different than having this

intended use.

MS. DeLUCA: When I look at the community that I live in, which is probably -- it's very rural, the churches are very large. People go there for their healthcare. They don't come into the city for their healthcare. So we have to send a doctor out. But mostly we send a nurse practitioner out. And it would be so nice to be able to have them have something like this that would be a definitive test and be able to give the prospective patient who may probably have never been a patient before the feeling that now they are and that they could have a medical home to go to as a patient and yet get the conversation going. Colon cancer is killing too many people.

DR. GALLAGHER: So, I'm going to go back to taking FIT out of the question and go back to the intended use and how to deal with it. I think, again, if the intended use is tweaked, I could easily see this as an alternative for FIT because I think continually doing this comparison between something that we have that's different and whatever kind of clouds the question. I mean, yes, we might want to make some other recommendations in terms of putting them together, but I also want to make sure we address the question separately.

DR. PRZYGODZKI: But what do you mean by tweaked?

DR. GALLAGHER: So, I'm thinking about rather than just for the general population, perhaps it is for those persons who are unable for some physical reason or cultural reason to do a colonoscopy or a FIT or something

like that. So, I mean, that could happen. Another thing could be, perhaps, that intended use could be narrowed a little bit in terms of the larger -- I guess the screening part is kind of throwing me off a little bit in terms of how big, wide that is. But I think, again, that intended use if it's tweaked in those kind of manners to say these kinds of people who might participate or those who have never participated in a colon screening program before and are unwilling to do something like that, those kind of comments in intended use would help me out.

DR. PRZYGODZKI: And you feel comfortable saying that because this is comparable to, in your mind, to FIT, works better?

DR. GALLAGHER: No. I'm removing FIT from the question --

DR. PRZYGODZKI: Okay.

DR. GALLAGHER: -- because for me that clouds it. I'd rather it -- I'm trying to focus on this test.

DR. PRZYGODZKI: Okay.

DR. GALLAGHER: Getting to combining it and everything, I think, is a different question than the original question.

DR. PRZYGODZKI: Okay.

Yes, please?

DR. HICKS: Terry Hicks from New Orleans. One of the issues I noticed -- that we seem to dance over, I don't think we ever got to the bottom of it, was Dr. Skates and the Sponsor and the FDA, we talked about

the specificity issue, because it's kind of been left out there in the wings. You know, I think it was asked what is a reasonable specificity number, where are we, and everybody danced around it. I mean, I want to know does the FDA have any -- do you have something more specific that you would consider a reasonable number for a screening test? Is there something that would -- you'd be below the bar, above the bar? What would you have to meet to be acceptable?

DR. TZOU: I do not think we can provide a particular answer for that question, so we're just interested in what's the Panel's view on the performance we have in hand.

DR. HICKS: Can you ask one of the -- either of the statisticians? Yeah, I ask both of you. I'll ask your opinion. Is there somewhere that when you're looking at studies, where is there a bar? Is there a line that you just go, wait a minute, that's not good enough?

DR. SKATES: It gets back to the -- this is Steven Skates -- back to the issue of the benefits versus the downsides. And a downside here to me is the fraction of people that are going to have -- not have colon cancer and get told that they have a positive test for colon cancer. And there's 20% of those. And the other issue that is a little vague here is the frequency with this -- just test. But there's a suggestion of doing it annually. So every year, 20% of patients are going to be told they have a positive colon cancer test. And yet of those positive tests, only 1 in 40 is going to actually have colon

cancer for this test versus, say, another test like the FIT test, 1 in 5, somewhere, 1 in 5, 1 in 7, of those that are positive are actually going to have colon cancer. So you're worrying a lot less -- you're providing a lot less -- essentially, many fewer, seven times fewer patients are going to be worried falsely by this -- by FIT and compared to the Epi proColon.

And you might say, well, that's worth it to pick up one cancer, and that's hard to balance that out, particularly as the recommended follow-up is the colon test. So it gets -- and that gets amplified by the frequency. So if it's once every five years, that's five times less people who are going to be worried than once every year. So I think one of the clarifications we need is what is the recommended frequency here. And part of what is the problem is that we don't have any longitudinal data, any repeat data, so we don't know what that repeat is going to do.

DR. PRZYGODZKI: That's true, but that will be subsequently in, I think, a third question or something to that effect, where we want it to go. But I want to bring the Panel back into the question itself. These are all fantastic points that are being brought forth, but let's address (b). If yes, and let's say, if it isn't, you know, just forget the "if yes," do the data support a screening with Epi proColon as a second-line option only in patients declining FIT, an alternative to FIT, or other options? I'm still having mixed messages, and I'm not really getting a crisp answer from the Panel.

DR. WECK: Well, my answer was crisp.

(Laughter.)

DR. PRZYGODZKI: Well, I'm getting hints --

DR. WECK: So I might just state it again --

DR. LIPKIN: My answer was crisp, too, yes --

DR. WECK: I think -- I mean, the question here is specifically asking us to compare this to the FIT test. So now we need to do that, and I would say that, in my mind, the FIT test performs better, so I would only consider it as a second-line option in patients declining FIT.

DR. PRZYGODZKI: Do others disagree from the Panel?

DR. NOSTRANT: I guess for those that answered -- oh, Tim Nostrant -- for those that said no, you can't even answer (b). It's only if you say yes to (a). So, therefore, the ones that say no can't even answer that.

DR. SKATES: So I think that's why it should not say "if yes."

DR. NOSTRANT: Okay.

DR. SKATES: I think --

DR. NOSTRANT: Okay.

DR. PRZYGODZKI: I'm looking at this as this is really more of a clarification point, and if Dr. Gutierrez sees that I'm way off base in stating this, I look at this as being a clarification for the FDA to make a decision at one point as well with our recommendation. Does this absolutely have to be "if yes" in the conditional? It seems no. Am I correct?

DR. GUTIERREZ: No, I would -- you're actually not even taking a vote on it, so yes, I would take it as --

DR. PRZYGODZKI: Excellent. Okay. So in that case --

DR. NOSTRANT: I would say -- I would have said (i), a second-line option, because I do agree that the specificity would be a --

DR. PRZYGODZKI: Okay. So does the Panel see anything other than a second-line option for this test? Does this sound adequate?

DR. LIPKIN: I think, you know, clearly the whole concept of the serum test is that it will bring some people in who have an aversion to touching their own stool. It's okay. So, you know, it's a cultural thing, and that's fine. So, I personally feel that as an alternative to FIT is fine, you know? You don't have to force someone to touch their own poop. It's okay if they don't want to do it, and the important thing is to bring them in and get them screened.

DR. McSHANE: Lisa McShane. So, I guess we ought to clarify then what we mean by second-line option. I was interpreting that as the patient would have to at least be asked if they would be willing to do the fecal test. And if they say no, then you offer them this test.

DR. PRZYGODZKI: Does that sound supportive of what the Panel's seeing?

DR. GATES: Yeah, I would -- not to get too Boolean about it, but I would say that it would be, you know, you offer one or the other and

they can pick which one they want to use.

DR. PRZYGODZKI: Okay. So the section (b) appears to be that -- would be two different types of approaches, either a FIT or the Epi proColon. If individuals would not want to do FIT, Epi proColon would be the one that would be supportive? Is that -- does that go along or no? I just want to have the clarification --

DR. McSHANE: Yeah, well, I guess, I mean, if you're offering them both choices, then there has to be an assumption they're being informed about the pros and cons, and if they pick the Epi pro, possibly one of those factors is that, yuck, I don't want to do the fecal test. So, I think there's a real blurring of what those two options actually are.

So, can we safely assume that if we put in the package insert that, you know, the patient should be -- it should be explained to the patient what the sensitivities and specificities are, and on that basis they --

DR. PRZYGODZKI: Um-hum. We will illustrate that --

DR. McSHANE: -- can decide how they want to balance those two factors.

DR. PRZYGODZKI: That actually will be illustrated in the -- I think it's, again, the third question.

MS. DeLUCA: I mean, we're talking about informed consent. So the informed part is assumed here, that they know, for example, that there may be some strengths in the stool testing --

DR. PRZYGODZKI: Well --

MS. DeLUCA: -- but you can get other pretty good information from this other option, so that if you're -- you don't want to deal with your stool, you can take that. That's -- I mean, we really are taking --

DR. PRZYGODZKI: I would only mention that as --

MS. DeLUCA: You're assuming --

DR. PRZYGODZKI: Yeah, assuming things. One can assume many different things. Anything is possible. It has to be relatively clear. And, again, I'm asking the Panel, is the assumption that both tests are open to the debate for the patient? Is it that one would go with FIT first and then potentially Epi proColon as a second? Or which one? Is there an issue with either or how?

DR. LIPKIN: Lipkin. I'll comment. You know, we're not -- we don't have complete data. We have somewhat sparse data here, and just answering this particular question, you know, this study was designed for --

DR. PRZYGODZKI: Sure.

DR. LIPKIN: -- at least the pivotal study was designed for -- asked another question. But given the totality of the data, and given that there will be some people who would just prefer for various reasons -- maybe it's even just, you know, they want to get out of the doctor's office quickly, you know? They say I can get a blood test instead of having to, without getting too graphic, wait an hour or something like this. So, you know, which

is fine. So, to me, the available data, the totality of the data says it's an alternative to FIT, and that's acceptable, at least from my perspective.

Just touching on your thing, this is a test -- this is not a genetic test. There is no informed consent. This is a test that's a check box. It's an epigenetic test. Not a genetic test. There is no informed consent, and it's something that people would just order. That's my interpretation.

DR. NOSTRANT: Were you going to use the equivalent? You said alternative, this is an alternative, just leave it in -- or are they equivalent? So, should you be saying to patients these tests are the same, pick one?

DR. LIPKIN: If you're asking my opinion -- Lipkin, again -- that it hasn't -- you know, I don't think we have data necessarily to demonstrate equivalence. We have some data on non-inferiority, so I personally kind of like the alternative in patients who don't want to do colonoscopy.

DR. NOSTRANT: But when you say alternative, do the patients understand what you're saying? You know, you can take cake or pie. Is there a difference? You know, what I'm saying is, are you going to delineate for them this test is better, that test is better, they're equivalent?

DR. LIPKIN: I think that's something for a physician to be able to attempt to at least explain to the patient. I would not call them equivalent, but I think certainly they're viable alternatives.

DR. NOSTRANT: Okay.

DR. PRZYGODZKI: So, they are assumed as not equivalent. And at this point, I would like to give Dr. Gallagher the ability to speak about this.

DR. GALLAGHER: Okay. So, if we leave the proposed intended use as is, then I would say it would have to be a second-line option. If we change the intended use or suggest that, then I would see it as an alternative.

DR. PRZYGODZKI: Dr. Nostrant, I see your microphone on.

DR. NOSTRANT: I was just going to recommend the same thing. I guess the only concern I have is that you have to answer yes to that if you're going to say the other two things --

DR. PRZYGODZKI: We described that. There was no issue about yes or no on this question.

DR. NOSTRANT: And I think the declining FIT means, I'd rather do a blood test is declining FIT, that it should be just equivalent. I don't -- and I think that's where the alternative comes in. I think that declining FIT means that you have to explain to them that FIT has a better specificity, and therefore, you're going to have less chance of getting a colonoscopy particularly if you're negative, which most patients will be. So, the argument would be -- is that you have to explain that to them, okay? And then they have to choose the blood test.

DR. PRZYGODZKI: Okay. Very good. So it seems like we've also touched a little bit on position (c), that is, based on the results of the pivotal

and supplemental clinical studies, do the data allow for adequate assessment of the benefits versus risks of Epi proColon. And there's, I think, a lot of debate along this line from what I've heard on the Panel, that there are certainly issues with specificity, sensitivity may be similar, and what would -- anybody would want to add to note to this, if this is adequate, not adequate?

Dr. Skates, please?

DR. SKATES: Steven Skates, again. I guess what troubles me, also, is that they set a bar for specificity, the Sponsors did, and they failed to meet that bar, and there doesn't seem to be any consequence from that failure in meeting the bar.

I think it was set there for an important purpose, which was to limit the number of false positives, and the downstream consequences of those false positives, which are multifaceted, including anxiety. But the spin here has been to say that, well, false positives, but they're going to end up with a colonoscopy, which is what is recommended anyway. I'm troubled by that flip in terms of setting a bar and not meeting it and then portraying that as a positive. I think there should be some holding of accountability to not meeting that bar. I'm not quite sure what that is.

I think something along the lines of -- you know, I guess you can't put this in the product insert, but seven times as many people will be falsely positive with test A compared to test B, or 20%, 1 in 5 of you without colon cancer will have a positive test, at least having that on the product

label, I think, is an important aspect and a downstream consequence of them not meeting that specificity bar.

DR. PRZYGODZKI: Dr. Gallagher?

DR. GALLAGHER: So, I'm going to agree with Dr. Skates on that one. I think -- so I've been pretty positive on the other -- on the (a) and (b), but I think (c) for me is the things that he said, but connected to that are the psychosocial risks that were not included in the risk factor consideration being missing.

DR. PRZYGODZKI: Please?

DR. HICKS: From the FDA, again, could we get -- I kind of missed today, it was kind of glossed over, too, about what risk, the definition of risk is here. Does it go beyond the -- if the test has no risk at all, you know, they draw the blood, you get a hematoma or something, but beyond that, the things that -- if it leads to a colonoscopy, is that tied to the mother ship, that any problem there happened because of this, or is it over? When we measure risk, what are we measuring? Just taking the blood and we're done, or is there something more to it downstream?

DR. TZOU: I think the relevant aspects of the process should be taken into account, if appropriate. So, if you're considering this screening process, it's not just the initial collection of the specimen sample, but also, what are the follow-up potential issues that arise from that.

DR. PRZYGODZKI: Package deal.

DR. NOSTRANT: Can I ask one more thing?

DR. PRZYGODZKI: Yes, please.

DR. NOSTRANT: I guess I would ask everybody to kind of think of one other question that you would ask a patient. What would you be more scared about? You have cancer now and we've missed it? Or you are going to get a colonoscopy because you may be positive for cancer? I would be --

DR. SKATES: Falsely positive?

DR. NOSTRANT: Falsely positive. Yeah. I would be much more scared about missing the cancer, which seems to be everybody is willing to agree to that, because that's the standard that we expect from a noninvasive test. But the argument is, is we're going to then compare that to doing 19,000 approved and most considered rational approach. So, it doesn't seem to fit with me about the psychological aspect, because I think the psychological aspect of having missed 30% of colon cancers, up to, but not probably above that, versus I might have a cancer that's there because I have a positive test, but I'm probably not going to have the cancer. So, I guess that would be my argument to this whole process.

So, I think that they've adequately showed sensitivity, but I don't think they've adequately showed -- you know, you're going to get more colon -- you're going to get more colonoscopies, no question. But the argument here is that we're talking about a patient population that likely has refused colonoscopy or is not taking it, because we've plateaued over here.

If we can get a few more in there, it's probably worthwhile. That would be my argument.

DR. PRZYGODZKI: Okay.

Dr. Hicks?

DR. HICKS: Yeah, my question would be for the fairer sex, I guess, the analogy would be for mammography. So, if you have a mammogram and we over-read it, which they do a lot, are you so freaked out, are you glad that at least they saw it and you got a biopsy, versus not at all, if it had more specificity to it?

MS. FURLONG: So, I think that's what I wanted to say about this, is that the anxiety is short-term because you're able to do something to confirm the negative, right? So I think in the -- if you didn't have an alternative to go to to confirm that false negative and say, actually, it was -- false positive, I'm sorry -- that, you know, I've had a colonoscopy, and I'm cancer-free. I think the anxiety is very short-lived, as in the over-read mammogram. And I think patients would be happier with that as opposed to missing a lesion.

DR. PRZYGODZKI: Okay. So having noted this, it seems to me that, based on the results of the pivotal and supplemental clinical studies, the data -- I'm still not sure.

(Laughter.)

DR. PRZYGODZKI: It's sort of --

DR. NOSTRANT: What risk haven't they showed here? We know the benefits. What risk haven't they shown?

DR. SKATES: Well, the benefit is what fraction are going to take the blood test that aren't taking any test at the moment. We have no idea.

DR. PRZYGODZKI: The part of the question that I'm not really certain of, when you look at the testing itself and the whole process, the higher the stage of the colorectal cancer, the more advanced the tumors, it appears to be that there's a greater percentage of positivity with Epi proColon, which is fantastic. Then when you look at the perspective of having triplicate tests, one of them being positive, and that one positive test shows that the whole deal is positive as well, after amplification of high number, you may be looking at a very small area within the colon that may have an alteration. And going in with a colonoscopy may or may not answer that question regardless, if you think about this. It may be a minor, small area, depending on how the individual wants to go through the thoroughness of a colonoscopy, and I'm not going to have anything against anyone doing colonoscopies, but there are variabilities of success rates within different physicians as well. And if this is a general population type of approach, it gives me pause to know that the question -- I get a result on a blood test that may be positive, and then I have a colonoscopy, and I have negative, and I have this lingering feeling of -- am I really positive or not. I don't know.

I could state this only for one simple reason, because I have

Crohn's, and I go every two years, and I've been doing this for 20+ year, and I wonder. And I always wonder, because I have that greater chance of getting colorectal cancer. Yeah. And it kind of makes me pause for a moment with this, too, so --

DR. HICKS: I have a question for Dr. Nostrant. I know a future study might really clear this up, but say I come to you and I'm recalcitrant to get the stool test. You draw the blood, it comes back positive. Would you, say, have me take the FIT test and see whether or not it was positive? Would that change your mind about scoping me, the combination of the two tests?

DR. NOSTRANT: No, it wouldn't because I'm also -- I think most people forget that even though the indication for colonoscopy is to screen for colon cancer, but we're not doing it for that reason. We're not in any way, shape, or form doing it for that reason. What we're doing it for is to look for advanced adenomas or precancerous lesions to prevent cancer.

DR. HICKS: Right. But if this test came back --

DR. NOSTRANT: That wouldn't have changed. I would have done the colonoscopy.

DR. HICKS: You would have -- you wouldn't give the stool test a chance?

DR. NOSTRANT: No.

DR. HICKS: And if they didn't match --

DR. NOSTRANT: Because we know that there's a false positive

rate, and it's going to become negative sometimes --

DR. HICKS: Not much, not much.

DR. NOSTRANT: Well, that's what they say in the -- well, the argument is I want to do the colonoscopy.

DR. HICKS: I mean, I think 97.4 is pretty good, so -- all right.

DR. PRZYGODZKI: So it seems to me, in summary, that this is a very -- there are very few aspects that are absolutely clear in consensus among the Panel in this subject on here, in (a), (b), and actually (c). It's more or less that the Panel is somewhat divided on aspects of this.

Dr. Gutierrez, from what you've heard, do you have specific questions that you want to ask?

DR. GUTIERREZ: Actually, perhaps there is just one clarification. So, clearly, the intended use was as stated. The company did add a limitation, and so I would like to hear a little bit of whether that -- how that plays into does the intended use need to be changed or not, or is that adequate enough to do the limitation. And if you need to, I can actually read the limitation if that would help. I had it a second --

DR. SKATES: Is it on the FDA presentation?

DR. GUTIERREZ: It is.

DR. SKATES: What slide?

DR. GUTIERREZ: 665 -- no, it's slide 8. So it says proposed limitations: Epi proColon is an alternative screening method for patients who

are at average-risk of CRC and who are unwilling, unable, or do not undergo screening by other recommended methods.

DR. PRZYGODZKI: Well?

DR. LIPKIN: Lipkin. I mean, it doesn't -- when I read No. 6 and No. 8, I think that 8 contradicts 6, you know? Six says I'm going to -- this is one definition, and 8 says, well, I'm going to carve out, you know, 20% or something of that. And that was the question I sort of asked the Sponsor before, you know, which is it? Or do we vote separately on both?

DR. PRZYGODZKI: This basically brings back the point (a) that was sort of a mixed bag.

Dr. Skates looks like you wanted to say something? Ah, okay.

DR. WECK: I guess I would just make one comment about the intended use. You know, I think it would read as in No. 6 because that's the stated intended use. So if we want to qualify it, the limitations should be --

DR. PRZYGODZKI: Can we see slide 6, please?

DR. WECK: -- part of the intended use, you know, as Dr. Lipkin mentioned. But I just would also caution that if a test is FDA-approved, even if it's for a specific intended use, there is the chance that it will be used for other than the intended use, so it would be used off-label --

DR. PRZYGODZKI: Absolutely.

DR. WECK: So, if it's thought to have reached the bar of being an FDA-approved test even for a particular indicated use, you know, there is,

of course, the chance that it would be used more widely.

DR. PRZYGODZKI: Dr. Gates?

DR. GATES: Yeah. I'd like to say that's not under purview of this discussion. I mean, all we can talk about is what the package insert says and what the intended use is as written.

DR. PRZYGODZKI: Absolutely. That's true. That's true.

DR. GUTIERREZ: So, yes and no, because part of the way we've asked questions is whether you need to add -- you know, whether there are mitigations -- if there's a high risk of misuse, you could try to put in mitigations, and we do ask the Panel somewhat of what kind of things you would like to add to the label that may mitigate things like off-label use. So that sometimes can come into the conversation.

DR. PRZYGODZKI: Yes?

DR. SKATES: Steven Skates. So, on this intended use, there are a few issues that I think need to be explicit. One is age and one is frequency. The frequency is quite important in terms of, to beat a dead horse, the false positive rate. The more frequent it is, the more your false positive is going to be an issue.

And for those, I want to push back a little bit on this issue that false positives are almost so minor that they are not comparable to missing someone who has cancer because they didn't take a blood test, or because they didn't take a test because it wasn't -- the blood test wasn't available.

There has to be some point at which you worry hundreds of people to find one case of cancer, where you say it's not worth it. And if there's not, then just -- then flip a coin and tell patients that they've got, you know, a positive test on that and get them motivated to go to colonoscopy. I mean, it gets to that point, where you must have -- draw the line somewhere at the false positive rate being a problem.

So, to summary, I'd like to see on the intended use an address of age limitations and whether that proposed limitations is actually in the intended use and then also what the issue is with frequency. That needs to be explicit.

DR. PRZYGODZKI: Okay. And that would be on the next question.

Does that answer your question, Dr. Gutierrez?

DR. PRZYGODZKI: Thank you.

So let us move to Question No. 2 now.

DR. LEE: Okay -- Sorry about that. Discussion Question 2: In the pivotal study, Epi proColon results in non-CRC subjects were affected by demographic factors, such as age and ethnicity. In addition to the proposed age limitation (that is, CRC screening guideline recommendations vary for persons over the age of 75. The decision to screen persons over the age of 75 should be made on an individualized basis in consultation with a healthcare provider), does the current data warrant one of the following with

respect to certain patient subgroups:

a. Additional labeling considerations (for example, warning, limitation) for patients who are above 75 years of age and/or African Americans?

b. Precaution about potential for increased false positive rate in patients who are above 75 years of age and/or African Americans?

DR. PRZYGODZKI: I think we can address both subsections together, and it may be overlapping here, at least from what I sense what the Panel was mentioning earlier.

Thoughts?

Dr. Weck? Oh, I'm sorry.

DR. WECK: So I would, you know, advocate a precaution about the potential for an increased false positive rate in older patients and in African Americans, you know. And in particular, we were talking about restricting the labeling intended use for people who were under 75. I just wanted to look at the age thing more completely, because on slide 29 is where the breakdown by age data are, and so the false positive rate was 16% in people who were between 50 and 59, and 26% in people who were over 70. But even in individuals who were 60 to 69, the false positive rate was 24. So I'm not sure why the line is being drawn at 75 here. It seems to me that the test has a much greater false positive rate even in individuals that are 60

and older, which is pretty young and which, I think, limits the, you know, use of this as a screening test. I don't know whether these are statistically significant, but there certainly seems to be a trend that the false positive rate was really only the lowest in people who were in their 50s.

DR. PRZYGODZKI: I think the age of 75 and above is basically just standards of other --

DR. WECK: Oh, the standard screening, okay.

DR. PRZYGODZKI: Yeah.

DR. WECK: But I guess I would say that I'm somewhat concerned about the increased false positive rate in individuals over 60 and in African Americans.

DR. PRZYGODZKI: Okay.

DR. WECK: Which I think should be included in the label.

DR. PRZYGODZKI: Dr. Lipkin?

DR. LIPKIN: Lipkin. Looking at the -- taking a step back and looking at kind of the totality of the data in the context of the scientific and medical literature, you know, in this trial, once again, we always have incomplete data, particularly in looking at subsets. The scientific literature has very strong data about methylation. So, this is the first epigenetic test; it's, you know, first DNA methylation test, and it is kind of a new frontier. The literature clearly supports that there is an age-dependent increase in methylation. And, in fact, sort of supporting that, just coincidentally, there is

a very robust p-value here. So that, given this one second kind of, you know -- hypothesis testing issue, and you know, it's there, but it's also at least supported by previous data in multiple studies.

The African-American issue is a little more complicated in my mind, because the p-value is not robust. We have this issue of, you know, if you're going to look at 20 safety signals, one of them is going to be positive with a nominal p-value of 0.05. And at least to my knowledge, I'm not an expert, but I guess I can take a quick look, there's nothing in the literature that I'm aware of about African Americans having higher methylation levels than other ethnic groups.

So, it's up to the FDA to decide what to do, but my opinion would be that the age-dependent -- and also, we know that 75, the benefit of screening overall diminishes. But the African-American is a little more complicated, and I'm not sure that the data is really that clear to support a limitation on that versus just a false positive, although it may well be true. We just don't know.

DR. PRZYGODZKI: But with respect to between 50 and 75, should there be additional restrictions on the label itself, in your opinion?

DR. LIPKIN: My opinion is above 75, there should be restrictions.

DR. PRZYGODZKI: Above 75, okay.

Dr. Nostrant?

DR. NOSTRANT: I'm concerned also -- above age 75, most of us are not screening, okay, at all, okay? And previously, most patients who are at 75 have already had colonoscopies, okay? It's the vast majority of them have already had that. The ones who are 75 are at a little higher risk, yes, but the false positive rate is also related to the risk of complications. The risk of complications at the age of 75 is almost two-fold greater, and that's one of the reasons why I think they chose that 75 age limit, because there is data of that, which is quite strong.

So, the argument would be is that we don't like doing colonoscopies on 75 year olds, so if they've had previously normal colons, even if it's 10 years since their last exam, we're very reluctant to consider that. And we tell the patients right off the bat that they are at a higher risk for developing complications. Now, if they're willing to accept that, we're willing to do the procedure, but the argument -- it's a tough sell for us, and we feel uncomfortable.

African Americans, I'm very concerned, because they have the lowest screening rate of all the ethnic backgrounds. So, I don't want to do anything to limit the screening of African-American patients. So, the argument is I wouldn't put the African Americans, but I would put the 75.

DR. PRZYGODZKI: Dr. McShane?

DR. McSHANE: I was going to make the same point about the African Americans. We've been looking at this risk/benefit tradeoff as, you

know, one benefit being we get people into screening who might ordinarily not come in, and since I'm assuming that the African-American population is what Dr. Nostrant said, is that they have lower rates of screening to begin with; so for that reason, I would agree. I would not put the restriction on African-American.

With regard to age, you know, to me, 75 is obvious. The question to me is should we go down younger or should we just have the data in the package insert and warn people that the older you are, the greater the chance of false positive and actually give them some of the numbers.

DR. PRZYGODZKI: Yes, Dr. Gallagher?

DR. GALLAGHER: So, I think that for African Americans, I don't think we should restrict anything based on this, but I certainly think that in the package inserts and other things, we need to let physicians and other healthcare providers know that they might see more false positives with that particular group of people. That's essential, because we don't want this also to turn into a case of usury in a sense that people would get these, and we know that they might go for more colonoscopies and whatever. I mean, they might take that incorrectly. So, I think we have to be really up front and inform people about that as well.

DR. PRZYGODZKI: So, if I may take a leap of faith, let me ask the Panel should we not restrict African Americans from this test, yet give

them the instructions that they have a greater false positive rate while taking the test? Is there anybody that's against that?

Yes?

DR. CAGGANA: Not necessarily against it, but I think if you put that from a newborn screening perspective, which is the other part of my life, when you tell parents or physicians that these are rare and that we have a high false positive rate, they tell the patient, oh, don't worry about it. The test really isn't that good. And we deal with that a lot in a screening realm. So, I would be hesitant to -- and I don't know the right way to prescribe it, but I would be hesitant to put it out there such -- so obviously, I guess.

DR. PRZYGODZKI: So, would that be more of a language thing that we would have to introduce that there is a greater false positivity because -- and this does not preclude you from needing to take additional steps in case --

DR. CAGGANA: Yeah, some caveat that you still would presumably send them for a colonoscopy, not blow it off because we know this test doesn't work as well.

DR. PRZYGODZKI: Okay. Dr. Skates?

DR. SKATES: I would just like to agree with Dr. Lipkin here, that in the African-American situation, the p-value is rather tenuous, and we're looking at multiple risk factors, and there was a hedge from the FDA. Just a Bonferroni correction would put it over 0.05. So I'd be very reluctant,

actually, to put a warning or restriction or even a suggestion that it's significantly high in African Americans. I think we need more follow-up studies before that goes in. I don't think the data support that very strongly.

Getting to Dr. Weck's point, I do think -- and I think Dr. Lipkin agreed about the strength of the p-value here, so I was -- at 60 to 69 and 70+, the rates are pretty similar. And what's different is the 50-year-olds, and they're much lower. So, I was surprised that Dr. Lipkin said 75 and above, when 60s are included here as a higher false positive rate. So, I'd be inclined to include that warning, or at least alerting of the physician that in patients higher than 60 -- and maybe there's a finer analysis that needs done, 65 or something, but 75 seems to be pulled out of the hat and not supported by the data.

DR. McSHANE: Yeah, and I agree about the fact that the ethnicity is a much weaker association. But I'd just like some clarification. You know, are you suggesting that you would not put the data even in? I mean, I agree. I would not give it as a strong, you know -- we found a significant result because people think significant means, you know, something -- or would you not even put it in at all --

DR. SKATES: I imagine these labels -- no, I wouldn't.

DR. McSHANE: You wouldn't.

DR. SKATES: I'd imagine these labels could be updated down the line with further data. I'd like to see this verified in more data, more

studies.

DR. NOSTRANT: Again, I would put the context here as risk versus benefit. Yes, there might be an increased risk, but that's also the highest big benefit we had group, 60 to 75, is when screening gives us the biggest bang for the buck. So, the argument is that I would not want to try to reduce that process. And particularly since the statistics are quite weak anyways to begin with --

DR. SKATES: Not for age.

UNIDENTIFIED SPEAKER: Not for age.

DR. SKATES: Age is strong, but ethnicity is not strong.

DR. NOSTRANT: Okay. I meant the ethnicity. Okay. I was meaning the ethnicity.

DR. PRZYGODZKI: Yes, please?

DR. LIPKIN: You know, just a quick cursory PubMed search, whatever it's worth, looking at ethnicity and methylation differences, there are, of course -- there are differences in the precise methylation, you know, points in different ethnic groups, but there's -- at least I can't find anything to show that there is, you know, increased methylation, for example, in African Americans. So I don't -- so that, at least, for whatever that's worth, argues against a limitation on African-American ethnicity.

DR. PRZYGODZKI: So, to some extent, is it appropriate to say that we do not need any additional labeling considerations, because there are

points about not noting specifically an African-American population, but potentially just addressing the 60 and above as having a greater propensity for false positivity, and that would be pretty much as crystalized as it could be?

DR. WECK: Right, putting that as information, either as a limitation or elsewhere in the package insert --

DR. PRZYGODZKI: Okay.

DR. WECK: -- not limiting the intended use, but there should at least be a mention that there is an increase in false positivity with older people.

DR. PRZYGODZKI: Is there also any need to add any other information into the label that folks here on the Panel are thinking about?

DR. SKATES: Sorry. You mean -- Steven Skates -- outside Question 2? I mean, because Question 2 is only age --

DR. PRZYGODZKI: Possibly --

DR. SKATES: So frequency. Is annual testing what is being requested as part of the intended use, because I don't think we have data on that --

DR. PRZYGODZKI: That would actually follow on Question No. 4, that part, but okay.

UNIDENTIFIED SPEAKER: That's Question 3.

DR. PRZYGODZKI: That's 3? Okay. I'm sorry. I'm getting --

there are a lot of questions and subsections in here.

DR. NOSTRANT: Might it be important to put this in a generic section on false positives, meaning that there's other things that are false positive, pregnancy and so forth and so on, other tumors, but you know, the argument here is that the real things we're really worried about here is the benefit versus the risk. You're going to do more colonoscopies in a population at risk for complications --

DR. PRZYGODZKI: Sure, sure.

DR. NOSTRANT: And that's really going to be probably only in the older patient. So, it may be, you know, somehow putting it as a generic -- and then at the bottom, put down patients over the age of 75 have a higher risk.

DR. PRZYGODZKI: Okay. Dr. Caggana?

DR. CAGGANA: Also, is it possible to put a caveat in there like you just said, you know, that there's a higher false positive rate in the, say, 60 to 75 age group, but we also pick up more cancers in that group or just some statement that says, you know, it is a risk/benefit?

DR. PRZYGODZKI: Okay. So Dr. -- oh, sorry, yes?

MS. DeLUCA: There's such a difference between, you know, in that table between 59 and 60. I mean, that's a big jump compared with between 69 and 70. I just think to myself, I don't know, 65 up might make more sense. I don't know what's happening between that 59 and 60 that

that cutoff is accommodating enough.

DR. PRZYGODZKI: Maybe --

DR. SKATES: I agree. This is Steven Skates. I think a little more finer analysis would give us a better handle on what that number should be, which is why I mentioned also 65.

DR. PRZYGODZKI: Okay. Dr. Gutierrez, does this answer your question for No. 2?

DR. GUTIERREZ: Yeah. I think we can move on. Thank you.

DR. PRZYGODZKI: Okay. Very good.

Question No. 3, then, please?

DR. LEE: Question 3: The proposed claims do not rule out repeat testing as part of the CRC screening program with Epi proColon. Cross-sectional performance at one time point was established in the pivotal and supplemental clinical studies. Follow-up longitudinal performance data on patients that tested negative with Epi proColon were not provided. The Sponsor has suggested a limitation (that is, there is insufficient evidence to report programmatic sensitivity of Epi proColon test over an established period of time).

a. Based on the available data, should the Epi proColon assay claims be limited to one-time screening?

   i. If no, please discuss whether a longitudinal study should be required to address long-term safety and

effectiveness.

ii. If yes, please advise if a longitudinal study should be optional.

b. The Sponsor has proposed a warning (that is, a negative Epi proColon test result does not guarantee absence of cancer. Patients with a negative Epi proColon test result should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests, and/or other recommended screening methods). Does this adequately address considerations (for example, time interval and testing method) in product labeling to assure safety and effectiveness for follow-up evaluation of patients testing negative with Epi proColon?

DR. PRZYGODZKI: Excellent. Thank you. So let's go at (a). Based on the available data, should Epi proColon assay claims be limited to a one-time screening? Yes or no?

Dr. Caggana?

DR. CAGGANA: Well, that's all we have data for right now. So I would say -- this is the same as the other question. I would prefer to require a longitudinal study before I make that difference --

DR. PRZYGODZKI: Okay. Okay. Yeah, I bring up -- I have to ask at least one individual, but it seems almost that there is a need to do

additional -- and this is additional testing longitudinally, yet there's -- this has data, but it's not enough. Is that the sense that the group gets? Please?

DR. BUJOLD: Yeah. Ed Bujold. I think definitely you would need more data, but you know, I'd also like to see, and it maybe would increase the sensitivity and specificity of the screening test, to have -- see what both tests do together, you know, those sort of tests. And maybe -- I know tomorrow you're talking about a stool-based test, but put all three of them --

DR. PRZYGODZKI: We can't speak about tomorrow.

DR. BUJOLD: Oh, I'm sorry.

DR. SKATES: Steven Skates. Based on the available data, the claims I think can only be limited to a one-time screening. Now, does that mean that the test can't be used once it's on the market for repeated screens? That, I don't -- it's unclear to me. I would like to see a longitudinal study. It would address a couple of issues. One is this dependence that the FDA highlighted. I think that's important. If it's dependent and the same people keep getting positive tests, that actually may be a good thing, because you could then rule them out and say, okay, after two positive tests -- or if we understand the biology enough and Septin9 is, in fact, methylated and remains methylated over time even in people without colon cancer, then once they get a false positive, and it's on colonoscopy, then they don't need another test. Who needs another test is those people that are negative. And

we only know that with a longitudinal study. So that nuance and what to do with follow-up, I think, is very important.

Another issue is that the calculations that were given by the FDA were based on prevalence, which is about 7 per 100,000. And that's partly because of the length of the preclinical duration of the disease. You get -- once you get into repeated testing, then what's important is the incidence rate, and that's about 1 to 2 per 100,000, so three times less, which means that the false positive rate is going to be even a bigger factor in longitudinal assays.

So, this issue of what is the programmatic sensitivity I think needs to -- it's crucial that we get data on it. So, I would say that longitudinal study should not be optional. It should be required. And the issue is what plane should be left standing. And certainly I think there's data here for a one-time screening, and the question is should we have -- allow repeat screenings, and I'm reluctant to do the repeat screenings, but I'd like to hear what the other Panelists have to say about that.

DR. HICKS: For negatives, if you're negative, would you continue to screen is your concern?

DR. SKATES: I was actually trying to show a positive result. If my understanding of the dependence study turns out the way I think it might, which is that if Septin9 remains --

DR. HICKS: Right.

DR. SKATES: -- and you keep getting a positive test on people that were falsely positive, and then the people that -- then they don't need colonoscopy --

DR. HICKS: No, but if you scope them -- so they come in and you're positive --

DR. SKATES: And you scope them --

DR. HICKS: You're done for 10 --

DR. SKATES: You're done for 10 years, yeah.

DR. HICKS: So I don't have to worry about it.

DR. SKATES: And I'd want to see that as part of the label or at least how the test runs out in sort of repeated use.

DR. HICKS: Yeah, because that'll affect the denominator as we go downstream after somebody's scoped.

DR. SKATES: Absolutely.

DR. HICKS: Right.

DR. SKATES: And we need data, longitudinal study, to address that.

DR. PRZYGODZKI: Dr. Nostrant?

DR. NOSTRANT: Well, I don't think you have any data that you're good for 6 to 10 years, because we know in colonoscopy you're not good for 6 to 10 years. It's not true. We miss 68% of cancers, early cancers, very early cancers. So we know that that's not true. It's the best we're going

to get, but --

DR. HICKS: But that's the data you have now.

DR. PRZYGODZKI: But to some extent --

DR. NOSTRANT: Yes.

DR. PRZYGODZKI: -- what I'm hearing right now is a discussion that's a little bit tangent to what we're actually trying to address. Is this test and the claims that are here limited to a one-time screening, yes or no, and if we are yes or no, do we want to do a longitudinal study? I mean, I'm getting mixed messages to some extent here.

DR. SKATES: I'm sorry if I wasn't clear.

DR. PRZYGODZKI: I'm sorry --

DR. SKATES: It's yes --

DR. PRZYGODZKI: Yes.

DR. SKATES: -- limited to a one-time screening, and yes, we do need a longitudinal study, so it shouldn't be optional. It should be mandatory.

DR. PRZYGODZKI: Okay. Excellent.

UNIDENTIFIED SPEAKER: Agreed.

DR. PRZYGODZKI: Yes, sir?

DR. LIPKIN: Yeah, Lipkin. Yeah, I mean, the only data we have are for a single point in time test. However, you know, taking the longitudinal view here, you know, if this test is, you know, approved, then

this is something that can be done in the -- if you had in the future when there is data on that specific topic. So, that would be my -- I would agree with Steven Skates.

DR. PRZYGODZKI: Okay. So, if I may ask the Panel, it seems that yes and yes, that a longitudinal would be appropriate? Does that seem to be more of the census of what the Panel has?

(No response.)

DR. PRZYGODZKI: Okay. Very good.

Let's take a look at part (b). The Sponsor has proposed a warning, and as you've seen, the warning there. Does this adequately address considerations, time interval, testing methods, and the like in this?

And the Panel, thoughts on that?

Dr. McShane?

DR. McSHANE: I think there has to be the warning. Does it adequately address considerations such as time interval and testing method, no.

DR. PRZYGODZKI: No?

DR. McSHANE: I think that has to be addressed in the mandatory longitudinal study that we're suggesting.

DR. PRZYGODZKI: Looking at the responses of the individuals around the table, does anybody have an objection to that statement?

Yes?

DR. NOSTRANT: Tim Nostrant. I think the warning has to be very specific, and what you're really about is the first sentence. It doesn't preclude cancer.

DR. PRZYGODZKI: Okay.

DR. NOSTRANT: Okay. And then you can put, I think, a second thing that a test can be false positive as well, as a warning, and that would be the only two things I would add, because we don't know whether or not you need to participate in further programs. We don't know that. So if we're going to use data to say that we don't know that.

DR. PRZYGODZKI: That's right. Okay.

DR. NOSTRANT: But the argument is, is that best opinion, or something like that, is that further follow-up is necessary by other methods.

DR. PRZYGODZKI: Okay.

Dr. Gutierrez, does this answer your question?

Yes, sir?

DR. TZOU: Thank you. I think there is a clarification between whether a longitudinal study is required, which I think we answered before, but whether, based on the current available data, what is appropriate advice concerning follow-up for labeling for patients, physicians, laboratories to have in hand based on the current available data. So, is this an appropriate statement now, or should there be some language of things to consider as far as when to follow up or how to consider appropriate alternative follow-up

testing, if there should be language or thoughts to help direct people based on in the absence of longitudinal data.

DR. PRZYGODZKI: Would that entail that a negative study would not preclude you from additional tests? Would that be something to that effect or --

DR. TZOU: So, I think Dr. Skates brought up one question as far as testing frequency. So, if the Panel thought this was, for example, more along the lines of annual FIT, would it be something like discussion regarding follow-up might be appropriate at a one year timeframe or something like that? The language is not exactly right, but just the general idea is would it be appropriate to say --

DR. PRZYGODZKI: Okay. I understand --

DR. TZOU: -- you need to revisit your screening options in a year, not to say necessarily what that is --

DR. PRZYGODZKI: Right, sure, sure --

DR. TZOU: -- so that would be one approach. Another approach would be, you know, we had the discussion whether we have this sort of hint about FIT. So, would it be appropriate to say, well, one of those options you should entertain is, for example, FIT, because we don't have performance repeat with this device, and then we -- those are just sort of general --

DR. PRZYGODZKI: Okay. Okay.

DR. TZOU: -- things whether the Panel thinks those are worthy to explore or not.

DR. PRZYGODZKI: Okay. Panel Members? Thoughts? Yes?

DR. McSHANE: Lisa McShane. I don't think there's a lot we can say, because we don't have data on any of this. I guess the one concern I would have is that if we just leave it as follow the usual stuff after you've had your -- you know, this test, the Epi proColon test, what we don't actually know is if those who are positive on this test and get a colonoscopy and turn out to be negative by the colonoscopy, if they really do have the same risk level as someone who never got the Epi proColon test, and therefore, didn't know if they were positive or negative, for which the standard recommendation would be 10 years if they were negative on the colonoscopy.

So, that just points to the reason that we need to have this longitudinal study and think carefully about how it would be designed. So I think we can't really do any better than being sort of vague on this recommendation. We just have no data to base it on. I think it has to be a discussion that you have with your clinician that --

DR. MAHOWALD: That's right. And that kind of wording could be added to this, "based on the recommendations of your doctor," something like that.

DR. PRZYGODZKI: So the wording would be to do --

DR. MAHOWALD: Because we're going to learn more.

DR. PRZYGODZKI: Okay. So the wording would be, at this point, to do what -- to do secondary reflex testing, to do additional consultation with your gastroenterologist?

Thoughts?

DR. MAHOWALD: Yeah. You could just add a phrase after what's there parenthetically, seems to me, you know, "based on the advice of your doctor." Couldn't you just add a phrase like that? I hate to hear myself saying that because it sounds so paternalistic, but --

DR. PRZYGODZKI: Yes --

DR. MAHOWALD: But we're going to learn more in the future, that's the point, and someone needs to continually be apprised of what we've learned and advise patients accordingly or introduce these possibilities.

DR. PRZYGODZKI: Well --

DR. WECK: Right. I guess it's complex, because the intended use that's stated is for screening, but you know, not written, there is that clearly the intended use would be to do annual screening or more frequent screening than a person is recommended to get colonoscopy, which is every 10 years. But we don't have data for that, so we do need the longitudinal studies to indicate whether, for example, annual screening, you know, would be effective.

So, you know, the only data we have are the one-time

screening, but that doesn't imply that doing it once every 10 years is appropriate. So, I think you have to -- you know, if it is approved, I think you have to word it carefully, and I like the idea of putting in a warning that recommended screening, you know, annually via the following tests or every 10 years is still recommended in people who test negative.

DR. PRZYGODZKI: So, essentially, testing by other modalities, as recommended --

DR. WECK: As recommended, yeah.

DR. PRZYGODZKI: However, whatever modality you're using would be at least a safeguard? Does that sound correct? I am not saying it's the best thing, but I'm saying, on the other hand, if you want to do FIT, you can do FIT, if you want to do colonoscopy, you do it once every 10 years, and that's the recommendations --

DR. SKATES: I like Dr. Mahowald's comment about adding a phrase in there to discuss with your primary care physician or physician.

DR. PRZYGODZKI: Okay.

DR. SKATES: I think that really is important and is missing from here.

DR. PRZYGODZKI: Okay.

DR. SKATES: But I think what they say is, other than that, is reasonable.

DR. PRZYGODZKI: Okay. Dr. Gallagher --

DR. NOSTRANT: Don't put in there the gastroenterologist, okay?

(Laughter.)

DR. NOSTRANT: For a couple of reasons. Number one, they're not going to come back to the gastroenterologist after a negative exam, okay? And they will come back to the gastroenterologist for a positive exam, and then we'll explain the exam. Our biggest bane of existence is a person who comes back having a negative colonoscopy and then has fecal occult blood testing or fecal FIT testing, and then we're forced to do another colonoscopy. And I can tell you, the false positive rate is a lot more than you think, okay, a lot more.

DR. PRZYGODZKI: Okay.

Dr. Gallagher?

DR. GALLAGHER: I just want to be cautious about always using the term physician. I think taking up Ms. DeLuca's comment is that it should be healthcare provider, because a lot of these things are now being done by mid-level providers, and we don't want to exclude them from these kinds of questions.

DR. PRZYGODZKI: Okay.

Does that answer your question?

DR. GUTIERREZ: Yeah, I think that that's a good job. Thanks.

DR. PRZYGODZKI: Very good.

So Question No. 4?

DR. LEE: Before reading Question 4, we would like to note that the inclusion of a question related to a post-approval study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan does not in any way alter the requirements for premarket approval and a recommendation from the Panel. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and before any post-approval study could be considered.

Question 4: Assuming that a longitudinal study is needed to evaluate performance of Epi proColon, please comment on the following:

a. Is comparison to a recommended CRC screening option (for example, annual FIT) needed to evaluate study results and to mitigate study limitations as currently proposed by the Sponsor (such as, controlling for incident CRC cases, lack of objective criteria for evaluating study results)?

b. Is the Sponsor's proposed post-approval study adequate to address the following issues?

    i. Performance (for example, the number of test negative to positive conversions, the diagnostic yield of significant findings, the predictive values, adherence to

screening and diagnostic follow-up);

ii. Performance across different clinicopathologic characteristics;

iii. Safety concerns (for example, in the Sponsor's proposal, subjects would forgo annual FIT screening during the study duration and repeat Epi proColon testing will occur annually);

iv. Appropriate study population (for example, general average-risk population versus average-risk population who are unwilling, unable or do not undergo screening by other recommended screening methods).

c. Are there any additional considerations that should be taken into account for the post-approval study?

DR. PRZYGODZKI: Okay. I'm sure there is going to be a robust discussion on this one.

Dr. Gates, would you like to give us your thoughts?

DR. GATES: No, other than I think a longitudinal study, you know, as I think we've agreed, is merited, and I think it's up to the Sponsor and the FDA to determine what, you know, the appropriate study is. I would just parenthetically, and I just don't know, there is good longitudinal data on FIT testing? That's true? Okay. But yeah, that's my only comment.

DR. PRZYGODZKI: Okay.

Dr. Hicks?

DR. HICKS: I think one of the most beneficial things that could occur from here despite a decision about this device is that there seems to be a recurring theme about lack of data, you know, from statisticians and all, you know, if we just had the data, and then if we just had the data. There seems to be a data void. And I think it would be beneficial to everybody involved that if we go and do the longitudinal study and other studies, that the two parties get together and make sure that -- so we don't have to do multiple layers of stuff, that we get down what's lacking. If we can tell them this is what we need to feel better about this, that would be a great accomplishment.

And I certainly agree with the longitudinal study --

DR. PRZYGODZKI: What do we need to do to feel better?

DR. HICKS: I think what we have to do better -- and again, it's amazing if you -- it'd be interesting to get everybody's wish list, but we've gone around the room, and everybody has come up and said, well, that would be a great thing. You just said if we had some data, but we don't have the data about that, or we don't have the data, and McShane, Skates, everybody, you don't have the data, good idea. So, anyway, it's just been data all day long we don't have. FDA goes "don't have it."

So I would just -- you know, because I'm -- you're on the cusp of some great science here. This is incredible. It's a new barrier that's being

broken, and it just -- it needs to be nurtured, but you need to come up with the right stuff, you know? We got to get the data so that we could confirm it and run forward with it, but it's kind of hard at this point with all these questions about lack of data. So that's my point.

DR. PRZYGODZKI: Dr. Nostrant?

DR. NOSTRANT: I think we have to compare it to another noninvasive test serially. So, I think that you have to have simultaneous FIT data and simultaneous Epi proColon testing at the same time. And that's (b), number (iii). I don't think you can stop the FIT testing. There has to be FIT testing throughout the entire three years of their evaluation and two years in their follow-up.

DR. PRZYGODZKI: Dr. Gallagher?

DR. GALLAGHER: Here we go again. So I think this time out I'm going to say I would like to see a three-arm design where we could look at the differences between the test we're talking about today, between FIT and between the combined for a longitudinal study to be able to really say what is beneficial and what is not.

DR. WECK: I agree. I was going to say the same thing. I mean, that's going to dilute the numbers in each arm, but I think, you know, there is a real potential to have a very effective or sensitive screening test by combining the two tests together, so I think that would be important to do.

And then outside of that, I think it's essential to compare this

directly to FIT test in a prospective study.

In terms of other data that are needed, you know, I think the ethnicity and age-specific data are two things which were lacking perhaps, particularly ethnicity. So, if possible, it would be good to answer that in a longitudinal study or additional study as well.

But I guess in terms of the indication for testing, you know, if the indication for testing is specifically in people who refuse to undergo the FIT test, I don't know whether you could get at that in the design of a longitudinal study as well.

DR. PRZYGODZKI: Dr. Lipkin?

DR. LIPKIN: Thank you. So you're looking this way. They were all raising hands that way.

DR. PRZYGODZKI: Sorry.

DR. LIPKIN: That's all right. So quickly, well, there are a lot of questions in terms of, you know, of follow-up, so I'll try to be sort of brief, and I think it's actually somewhat beyond what the Panel can sort of do today. So, you know, in terms of a longitudinal study, in my mind, I mean, the point is that, you know, if this test were for pancreatic cancer, we wouldn't probably be here. We'd just say, there's nothing else, great. But we do have options. We have standard of care. So, it has to be really against the standard of care, and I think the comparator we're talking about here is FIT. That's my opinion. Whether it's a two-arm or a three-arm study, I think, is a

longer term discussion between the FDA and the company of what is sort of possible, what their willing to do, you know, what's appropriate. But at the very least, I think a two-arm study is important, and it'd be nice if they can do it, but that's, once again, I think, sort of beyond what we can just finish today at 4:17 in the afternoon.

And then in terms of some of the other issues, I think, given there is this issue of African-Americans, it should be, you know, addressed, statistically sort of addressed in terms of power. And then age, too, is the other sort of -- I put as the minimum.

After that, I think it's sort of, once again, sort of really up to the discussions between the Sponsor and the Agency to sort out, really, the precise detail.

DR. PRZYGODZKI: Dr. Skates?

DR. SKATES: So, I would agree with Dr. Gallagher that the ideal longitudinal study would be a three-arm study comparing FIT, Epi proColon, and the combination. And I guess the limiting issue there, presumably, is capacity of the company to do it, but scientifically, I think that would be the better study to do.

Then the other issue is (b) part (iv). I would think that that creates a pretty big barrier to getting accrual to this study and that a smaller side study may -- this is a three to five year study, longitudinal study, we're talking about, and I think that should be open as much as possible. To

answer the question about are people more willing to take a colon cancer test if a blood test were available, I see that as a small side study in a general population that might last six months, maybe a year at most, and you'd have the answer to that particular question. And it would allow this study to be open to the broadest possible population and make it easier for the Sponsor to do the study.

So, I see trying to combine the two studies, two questions into one study -- making it much more difficult for the Sponsor to do it. And hopefully that makes the longitudinal study easier to accrue to and quicker to do.

DR. McSHANE: Although, logistically, you might actually be able to do it in the same study if you viewed the side study as a run-in period to this one, because you start bringing them all in, and some people, when you offer them participation in the study, are going to say no, because I would never do the fecal test. And so you might be able to somehow use that as a run-in. And then after you've gotten your answer to that, then you just keep going with those who agree to be randomized.

DR. SKATES: Yeah, okay. And that's fine. I mean, I think the details, as Dr. Lipkin said, are beyond this Panel, but I want to -- I see (b) part (iv) as a very restrictive way to -- in accrual and just making the study very long, and I'd rather not that occur.

DR. McSHANE: Yeah, no, I agree. And I think that that

question (iv) is actually a really important question, because we've been arguing all along here that one of the rationales for having these alternative tests is because there would be a lot of people who won't want to do the colonoscopy. So, I do think it's critical to get that answer.

DR. PRZYGODZKI: So it seems to me that there's the thought of either doing a two- or three-arm study. There is the need to address ethnicity. There's the need to address age. Anything else that would be needed to be addressed?

DR. CAGGANA: Yeah, the population, and also --

DR. PRZYGODZKI: Ethnicity, right, I'm sorry.

DR. CAGGANA: -- be important to potentially address other outcomes since we have this information about that a Septin-positive test occurs in other cancers. So, maybe we need to do that follow-up, not just review records for colon cancer outcomes.

DR. PRZYGODZKI: Okay. So what you're saying is colon cancer and any other cancer?

DR. MAHOWALD: And I think it's important to recognize that ethnicity goes beyond African-Americans.

DR. PRZYGODZKI: Absolutely, absolutely.

Dr. Gutierrez, does that answer your questions?

DR. GUTIERREZ: Yeah, I think that's sufficient.

DR. PRZYGODZKI: Very good.

I'm sorry, there was a question here or --

DR. HICKS: Yeah. I just wanted to say two points. One, when you do the study about preference -- I agree that could be done in a short period of time. It would be absolutely imperative, though, that how this is presented is locked in stone. You know, you don't say, would you rather have this or that. I'm thinking you got to give them the information about the two tests, whether it's written down in a plastic diagram or something, you know what I'm saying? So that's one issue.

And the other issue is that -- which we didn't get to go back and visit, but Dr. Skates had earlier talked about with me -- we were having the discussion here about the consequences of false positives. We just kind of said not a big deal and everybody kind of moved on, but I think you had some concerns, and I don't know what data you'd want to collect about the false positives and its effect.

DR. SKATES: So, I'm assuming that this longitudinal study will collect similar data to what was done at the cross-sectional one-time study, which is what fraction followed up by colonoscopies as a gold standard are false positives from FIT, from Epi proColon, and from the combination, and what those rates are and how they change from one year to the next. And you know, there will be pluses and minuses there. Dependence could be very important in limiting the false positive rate in years two and three. The lower incidence can increase the -- or the effect of any false positives in years two

and three or subsequent to that, so --

DR. HICKS: Also risk, you mentioned risk.

DR. SKATES: So, well, I'm trying to recollect here, but the --

DR. HICKS: Well, the numbers of scopes that would entail a possible risk --

DR. SKATES: Yes, so --

DR. HICKS: -- and the emotional factor also.

DR. SKATES: That's right. The FDA did bring up the issue that additional --

DR. PRZYGODZKI: But these -- okay.

DR. SKATES: The additional detection that you gain through Epi proColon does generate additional diagnostic colonoscopies, which come with a certain amount of attendant risk. And there were four -- per colon cancer detected, there were four adverse events at a 0.68% right now. They weren't, according to Dr. Nostrant, they're very unlikely to be colon perforations. So what those adverse events were and how they balance out with the one colon cancer detected, probably it would be helpful to get FDA to clarify that.

DR. PRZYGODZKI: Okay. While this is very interesting, I would like for us to move ahead since Dr. Gutierrez is -- the question has been answered for him.

So, at this point, I would like for the FDA summation,

comments, and clarifications.

DR. LEE: Thank you very much for weighing in on these complex issues and questions regarding this PMA for the Epi proColon test. Your input based on your individual expertise and experiences has been greatly appreciated. So thank you very much for your time and your input.

Can I just make one more remark?

DR. PRZYGODZKI: Sure, absolutely.

DR. LEE: So, I would just like to note also that when you are voting on the ballot voting questions, to please consider the premarket data that has been presented in the Panel packets as well as the data that was presented and discussed today. And also please consider -- or please interpret the voting questions literally in the context of the proposed intended use, as I believe after the vote there will be an opportunity to provide further comment on how you voted.

So thank you.

DR. PRZYGODZKI: Excellent.

Now I would like to ask the Sponsor to present your views. You have 10 minutes.

DR. TAAPKEN: Thank you. Also, I would like to thank the Panel Members for their deliberations. However, if I may, I would like to make some clarifying remarks, because I had the impression that here and there, there was still a little bit of misunderstanding on certain points with respect

to the issues that were raised, and I hope I will be able to clarify the issue and reiterate how we see risks and benefits of this product being used in practice.

Now, the false negative rate that was discussed, we are talking about 70% sensitivity in a test that will be able -- in a population of 1,000 people pick up, from the seven cancers that are around, five cancers, at the expense of about 200 colonoscopies that will be done. That's sort of the ratio of the things that we're discussing here. There were some other numbers mentioned before. That translates to 99.77 negative predictive value in respect to the absence of colorectal cancer, with negative test results, which in our view, is to be seen as a relatively safe confirmation of the absence of cancer, and it's certainly better than not being screened.

I want to reiterate this point, and I have been asked about the data that we have generated or whether we have generated the data. In fact, we have studied preference and choice by patients in a small study that we did in Germany with 160 individuals. I have not presented the data here before, because of the fact that these were done in a different country with a potentially different setting. But, by and large, the data that was generated there was very straightforward. They were family practitioners that were basically asking individuals that went in in screening-eligible age, which in Germany is above the age of 50. And they were asked to provide the patient with a strong recommendation to undergo a colonoscopy.

Now, we don't have that kind of a guideline or not that strong

of guideline in Germany suggesting that. However, based on that recommendation, 38% of the patients followed that instruction and recommendation. 62% chose not to. In a second step, those patients were asked whether they would accept a blood test or a stool test, and they were offered the choice between Epi proColon and a FIT test. And about 85% of these patients chose and elected the blood test.

So, it is our belief that based on this, I would say, at this point, it's maybe still anecdotal data that we want to enhance in the context of a potential post-approval study, that this data hints that it should be possible to address the issue of lack of compliance with colorectal cancer screening in a quite effective way with a blood-based assay. The ease of use for the patient, the fact that patients are used to doing blood tests, that they go to the -- they do the lab work, they get blood drawn to do everything. Somebody was mentioning the fact they're just checking a box. I think that is a strikingly easy thing to do in the context of somebody refusing to get tested.

Now, do we believe that missing 2 out of those 7 cancers that are in these 1,000 people is a risk? It sure is a risk compared to finding them all with colonoscopy or other more accurate methods. But I would also like to point you to the fact that, at this point in time, in our view, with this 99.77% negative predictive value, we do not have many tests out there that have a comparable ability to rule out the presence of cancer right now. The

tests we have out there, the fecal immunochemical test, as I mentioned earlier, they are not consistent. There are different manufacturers selling different products on the market with performances that have been reported in the literature between the low 50s and high 80% ranges, none of which are -- I wouldn't say none of which, but many of which have not -- data have not been generated in truly prospective studies.

I think we deserve a certain level of credit for having done this kind of work, the prospective, fully evaluation of this product that we are presenting here today, and also, in a very comparable setting, the test of the non-inferiority to our test to what we believe is the best available FIT device on the market.

I understand your concern about the potential false positive rate. That is, of course, a concern that is always present with any test that delivers positivity rate, which is seen as significant. We have that situation, as was described, in mammography. We have that situation in many other tests. We have that situation, for example, in recently recommended lung cancer screening tests, where there is a 70% specificity. However, the U.S. Preventive Services Task Force has defined that this is a useful thing to do, because lung cancer is a severe disease. And even though 30% of those patients screened would have to undergo further analysis in order to make a confirmation of that screen, it was seen that lose-dose CT screening at that specificity range is something that makes sense.

I would like you to consider, also, that an 80% specificity at a 70% sensitivity is, in our view, not the perfect test, certainly not, but it has a significant value in its ability to help solve the problem of colorectal cancer being addressable, or as Dr. Johnson would have said, in order to close the gap, because we are convinced that 23 million people unscreened in the United States and about 53,000 patients or more dying each year from the disease is not a situation that is sustainable. And given the plateauing effect of the screening methods that have been implemented, quite successfully, I must say, because here, with about 60, 65% screening success, you're much better off than in many other countries. However, that gap, to reach the 80%, is a surmountable gap.

The number that I would like to provide you also with, the question was raised how many of these unscreened patients of 23 million patients do have access to healthcare. According to the literature we have available, it's about 75% of those that would actually have access to healthcare. And it is also clear that it should be possible to reach higher levels of compliance to screening, because we see that in other modalities and other screening programs for other diseases, where tests are available that are convenient and where patients have choices between tests that enable them to actually get screened.

So, I kindly ask you to consider this in your deliberations, and I would -- and, of course, I would like to close also with a statement: We as a

manufacturer are firmly committed to support this test, if approved, with additional studies to generate the kind of longitudinal data that, of course, no screening assay can provide at the point in time when it's introduced to the market. This kind of long-term data has to be generated, and again, we are committed to work with FDA to come up with the right protocol to make the right study in order to make sure that there is appropriate use in the context of screening for colorectal cancer.

Thank you very much.

DR. PRZYGODZKI: Before we move the Panel to vote, I would like the nonvoting members to express their views.

Ms. Furlong, from Consumer Representative, your thoughts?

MS. FURLONG: Thank you. So, again, as a consumer, I feel that there are people who will refuse colonoscopy or delay colonoscopy for a variety of reasons, some of which are based on resources, education, cultural philosophy, religious philosophy, and I think those individuals deserve some options. And I think that this provides that option to them and gets them likely into the colonoscopy, which is standard of care.

So, I do feel that this is a significant option or a worthwhile option to approve. I don't disagree that we need more data over time, and I think that is necessary and should be generated. But I do think this would be a welcome tool in the arsenal of tools against colorectal cancer.

DR. PRZYGODZKI: Thank you, Ms. Furlong.

Ms. DeLuca, our Patient Representative?

MS. DeLUCA: Thank you. My feeling is that we could gain a lot more in terms of the general public coming face-to-face with colon cancer as a possibility in their life that they're not now looking at. I think they see it as benign. I think they see it as something that they can ignore. And this isn't the case. And I also look to seeing the way that medicine is heading, doctors are being overwhelmed with doing tests and colonoscopies, and that nurse practitioners and doctors coming into this scenario are doing things that used to be done by a gastro in terms of a outpatient setting in a rural area. And I think that this test would fit in very nicely and getting us much closer to having 80% of people screened by 2018 instead of 65, where we are now. I think we could really close that gap well.

DR. PRZYGODZKI: Thank you, Ms. DeLuca.

Dr. Gates, our Industry Representative?

DR. GATES: Yeah, I tend to agree with my comrades here. I think this is a unique test in a couple of different ways, and in terms of being the first one to be able to offer a totally different specimen modality, blood testing, which I think has a lot of advantages, which I think we've talked about. Also, by the fact that the reflex of this test, in terms of, as we've discussed, specificity goes to the standard of care, and the fact that that standard of care is something we're all trying to get to seems to me to mitigate, to some extent, the specificity issue, that, if nothing else, we're

pushing people into something that's probably more accurate.

In general, the sensitivity doesn't bother me specifically, because I don't think there -- in terms of noninvasive testing -- there's anything better, and apparently there's data to support the use of a sensitivity at that level for FIT test that's accumulated over time.

I think there are legitimate issues in terms of specific data that needs to be presented to support specific issues in terms of the patient profile and those sorts of things, but I think it's possible to do a post-approval longitudinal study that'll address all those things. So from that perspective, I think it's a test that's worth approving.

DR. PRZYGODZKI: Excellent. Thank you, Dr. Gates.

So now we're ready to have the Panel to vote on the recommendations to the FDA for Epigenomics Epi proColon. Panel is expected to respond to three questions related to safety, effectiveness, and benefit versus risk.

Ms. Waterhouse will now read three definitions to assist our voting process along with the proposed indications for the statement of this device.

Before you go, there's a question.

DR. HICKS: Yeah, I just have one question before we vote. The product, if it's voted thumbs up on this, the way that it's worded, the proposed intended use, that's how it will come out, because I wonder what is

that relationship, then, with people who organize -- who write guidelines? I mean, are we going above them or around them, you know?

DR. PRZYGODZKI: We are --

DR. HICKS: I mean, you're saying that it's indicated for screening -- it's a -- so we're saying it is a screening test, it's okay to do it? You know, like, the people -- say just everybody else, ASCR, say everybody who writes guidelines, are those committees going to be hamstrung by that or not? They can choose to -- I mean, we okay it, we say it's okay for screening. Then what happens if it's in space and both of them go no?

DR. PRZYGODZKI: Well, one needs to realize that we're recommending -- we're sending a recommendation to the FDA, and FDA has to go through the motions that are necessary to uphold everything as it ought to be.

Is this correct?

DR. GUTIERREZ: Yes, that's correct. I mean, guidelines are written -- for example, the FIT test was never cleared for what it's being used for, so practice of medicine and guidelines are a different subject altogether.

DR. PRZYGODZKI: Okay. Great. Thank you.

DR. McSHANE: But I do -- really to clarify this, so we have to vote on these questions literally, so the intended use that I have in my packet here is on slide 6, and then on --

DR. PRZYGODZKI: You are voting on what you've heard and

what you have in your packet.

DR. McSHANE: Okay. But on slide 65, there's a Sponsor's proposed limitation, and there was a lot of discussing surrounding that limitation. So when I cast my vote for these questions, am I going by what's on slide 6 or what's on slide 6 plus 65?

DR. PRZYGODZKI: You're looking at the entire package.

DR. WECK: I think it's slide 6, the proposed intended use as written in the --

DR. GUTIERREZ: That's correct. You're voting on the intended use as written.

DR. McSHANE: On slide 6 alone?

DR. GUTIERREZ: With the limit -- I mean, they are proposing limitations and the rest, but it is in the intended use as written.

DR. WECK: So slide 6 through 6, basically.

DR. McSHANE: Six through 8, okay. That was my question. So it's not just slide 6. It's -- because it says proposed. I didn't know if that was just for discussion or if that was considered part of the intended use. Okay. So I take all three slides as what I'm voting on, the whole package?

DR. PRZYGODZKI: Really you're looking at the entire package --

DR. McSHANE: Okay.

DR. PRZYGODZKI: -- as well as what was presented.

DR. GUTIERREZ: And just to remind you, you have a chance

after you vote to -- if your vote was based on, you know, just intended use, but you think that you would have voted differently, you can, after you vote, you can actually explain why you voted and how you voted.

DR. PRZYGODZKI: So, shall we proceed?

DR. SKATES: So, can I get a clarification on that? Does everyone vote, and then everyone explain or you vote and then explain and it goes onto the next person?

DR. PRZYGODZKI: We all vote --

MS. WATERHOUSE: I'm going to go through the whole procedure.

DR. PRZYGODZKI: Okay. There you go.

MS. WATERHOUSE: All right. The Medical Device Amendment to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is a reasonable assurance that a device is safe

when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indications for use:

"The Epi proColon test is a qualitative in vitro diagnostic test

for the detection of methylated Septin9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the target DNA sequence in the promoter region of the SEPT9_v2 transcript has been associated with the occurrence of colorectal cancer. The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin9 DNA target.

"The test is indicated to screen patients for colorectal cancer who are defined as average risk for colorectal cancer by current screening guidelines. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. Men and women 50 to 85 years of age were included in Epi proColon clinical trial. The Epi proColon test results, together with the physician's assessment of history, other risk factors, and professional guidelines, may be used to guide patient management.

"The Epi proColon test is for use with the Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument."

Please use the buttons on your microphone to place your vote of yes, no, or abstain for the following questions. I'll read one question, and then you cast your vote, and then we'll move on to the next question once everyone has voted.

So Voting Question 1: Is there reasonable assurance that Epi proColon is safe for use in patients who meet the criteria specified in the proposed indications?

Please vote now: yes, no, or abstain.

(Panel vote.)

MS. WATERHOUSE: Okay. Voting Question 2: Is there reasonable assurance that the Epi proColon is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now.

(Panel vote.)

MS. WATERHOUSE: Voting Question 3: Do the benefits of Epi proColon for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now.

(Panel vote.)

MS. WATERHOUSE: Please give us a moment as we tally and verify the official votes.

(Pause.)

MS. WATERHOUSE: On Question 1, Dr. Mahowald voted yes; Dr. Weck voted yes; Dr. Lipkin abstained; Dr. Bujold voted yes; Dr. Hicks voted yes; Dr. Caggana voted yes; Dr. McShane voted yes; Dr. Skates voted yes; Dr. Nostrant voted yes; and Dr. Gallagher voted yes.

On Question 2, Dr. Mahowald voted yes; Dr. Weck voted no; Dr. Lipkin voted yes, Dr. Bujold voted no; Dr. Hicks voted no; Dr. Caggana

voted yes; Dr. McShane voted yes; Dr. Skates voted no; Dr. Nostrant voted yes; Dr. Gallagher voted yes; and for the tiebreaker, the Chair voted no.

For Question 3, Dr. Mahowald voted yes; Dr. Weck voted no; Dr. Lipkin abstained; Dr. Bujold voted no; Dr. Hicks voted yes; Dr. Caggana voted yes; Dr. McShane voted yes; Dr. Skates voted no; Dr. Nostrant voted yes; and Dr. Gallagher voted no.

So on Question 1, the Panel voted 9 yes, 1 abstain that the data shows that there is reasonable assurance that Epi proColon is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 5 yes and 5 no, and the tiebreaker from the Chair was another no, so 6 noes, that there is reasonable assurance that Epi proColon is effective for patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 5 yes, 4 no, and 1 abstain that the benefits of Epi proColon outweigh the risk for use in patients who meet the criteria specified in the proposed indication.

Voting is now complete.

DR. PRZYGODZKI: Okay. Point number 2 needs to be discussed so the Sponsor and FDA understand where we stand on this. I open to the group; basically state why yes or why no. A handful of individuals, probably, are more than adequate.

Dr. Hicks, let's start with you.

DR. HICKS: I think the issue was the amount of data that questioned, including the FDA's data and our statisticians' data, about documenting the effectiveness of the device.

DR. PRZYGODZKI: Dr. Bujold?

DR. BUJOLD: I would really agree with what Dr. Hicks has said, and the issues about specificity versus sensitivity and screening tests in general.

DR. PRZYGODZKI: Dr. Lipkin?

DR. LIPKIN: I voted yes on this, but I just want to give the caveat that, specifically, I really think it needs to be more clearly stated that this is -- and I use the word actually that's used, I guess, by the Sponsor as just an alternative to other testing. So I voted yes, but I'm still a little uncomfortable with this just indication of a broad indication for all Americans over 50 who meet the inclusion criteria.

DR. PRZYGODZKI: Dr. Weck?

DR. WECK: Yes. So I voted no. And, in particular, I think for the proposed intended use as a broad screening test for people of general risk, I'm uncomfortable with not clarifying that, that it should be an alternative for people who are not willing to take the FIT test. So if the proposed intended use were changed, I might be more willing to vote yes.

But I'm also, you know, uncomfortable, I think, with stating this is an effective screening tool for two reasons. One, because of the sensitivity

data, and two, because there is another test, that this did not perform better than, that's currently in use.

DR. PRZYGODZKI: Dr. Mahowald?

DR. MAHOWALD: Oh, yeah. In some ways, you know, the way the question is worded -- I'm sorry for forgetting again -- the way the question is worded allows for different interpretations. Is there reasonable assurance that the proColon test is effective for use in patients who meet the criteria? I believe there's reasonable assurance. It could be more compelling through better data if we had better data, and it would be desirable certainly, and I think everyone agreed with that, to obtain the data. But I think from at least my understanding of the data that we have heard, there has been some documented effective use in patients who meet these criteria. And so I voted yes.

DR. PRZYGODZKI: Thank you.

Dr. Gallagher?

DR. GALLAGHER: So, based on the fact that we were asked to use this -- you know, the slide plus the additional limitations in the thing, then I could vote the way that I did, but I think I would be much more comfortable if those limitations and whatever were worked directly into the proposed intended use rather than remaining outside of it.

DR. PRZYGODZKI: Dr. Nostrant?

DR. NOSTRANT: I still am very confused about how you define

effectiveness. I'm very concerned, because I do not, in my opinion, think that there's any difference in the performance of this test between safety and effectiveness. So, could someone define for me from the FDA what effectiveness means?

DR. PRZYGODZKI: We actually had the definition read.

DR. NOSTRANT: I read that, and what she read is the same as safety. It's no different than the safety issue. So, therefore, I still have the same difficulty, so -- but I voted yes.

DR. PRZYGODZKI: Dr. Skates?

DR. SKATES: So, I voted no on Question 2, because I saw the large argument from many people, but the Sponsor in particular, saying that part of the effect here is that no test, no detection, and that this was going to -- the effect of this test was going to get more people into it. And we had no data on that. And I could not, in good conscience, say there was reasonable assurance to say that it was going to be effective.

The other issue that I had problems with was Discussion Question 3 about the -- I thought we all felt uncomfortable about this being a repeated test. And the intended use didn't clarify that. And we were comfortable with the one-time screening test, and I would have been comfortable with that, because it would have had a very limited -- it would give some data, it would give some experience, but it would limit downstream negative consequences. So for those two reasons, I said no.

But, you know, there is room there, I think, for --

DR. PRZYGODZKI: Oh, sure. Thank you.

Dr. McShane?

DR. McSHANE: So, I voted yes the whole way across, and the only reason that I was willing to do that is that I viewed the proposed warnings and proposed limitations as integrally tied with the intended use. So I hope that was the correct way to interpret, and that was why I asked for the clarification initially.

You know, with regard to have shown effectiveness or not, you know, I think Dr. Skates makes an excellent point. I guess my sense, from what I heard, is that if you already have the patient in your office, it is likely you can just check the extra box, and they'll do it. But I do strongly believe that, you know, in all good conscience, we have to do this study, the additional longitudinal study that was proposed. I would feel very bad about this decision if that extra study were never done.

DR. LIPKIN: I support that assertion, too.

DR. PRZYGODZKI: Dr. Caggana?

DR. CAGGANA: That was my assertion also. I also went with the reasonable assurance and the effectiveness on the data that was presented, and then the caveat on the intended use and the longitudinal study. That seems like it's -- you know, we all agreed was going to be done.

DR. PRZYGODZKI: I voted no. There isn't much more to add to

the folks that have actually said no. I think there's a lot more data that's needed to be really supportive to sway an individual like myself to say yes. Does not mean that there's an incredible shortcoming with this, but just for need, yes, unfortunately, yes -- no. I'm sorry. Oh, boy. Long day.

Anyhow, so with this, I'd like to thank the Panel, FDA, the Sponsors.

And, Dr. Gutierrez, do you have any final comments?

DR. GUTIERREZ: No. I would also like to thank the Panel. This has been tremendously helpful. I'd like to thank the Sponsors, actually. I thought they did a very good job and presentation. And I'd like to thank the FDA team that put everything together.

DR. PRZYGODZKI: Thank you. And with this, today's meeting is over. Thank you.

(Whereupon, at 4:58 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

MOLECULAR AND CLINICAL GENETICS DEVICES PANEL

March 26, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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